# WORLD DRUG TRAFFIC AND ITS IMPACT ON U.S. SECURITY

## HEARINGS

BEFORE THE

## SUBCOMMITTEE TO INVESTIGATE THE ADMINISTRATION OF THE INTERNAL SECURITY ACT AND OTHER INTERNAL SECURITY LAWS

OF THE

## COMMITTEE ON THE JUDICIARY UNITED STATES SENATE

NINETY-SECOND CONGRESS

SECOND SESSION

**PART 5**

**RESEARCH ON MARIHUANA AND HASHISH**

SEPTEMBER 18, 1972

Printed for the use of the Committee on the Judiciary

U.S. GOVERNMENT PRINTING OFFICE

82-848 WASHINGTON : 1972

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402 - Price 45 cents

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# WORLD DRUG TRAFFIC AND ITS IMPACT ON U.S. SECURITY

MONDAY, SEPTEMBER 18, 1972

U.S. SENATE,
SUBCOMMITTEE TO INVESTIGATE THE
ADMINISTRATION OF THE INTERNAL SECURITY ACT
AND OTHER INTERNAL SECURITY LAWS
OF THE COMMITTEE ON THE JUDICIARY,
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 10:30 a.m. in room 2228, New Senate Office Building, Senator James O. Eastland (chairman) presiding.

Present: Senators Eastland and Gurney.

Also present: J. G. Sourwine, chief counsel.

The CHAIRMAN. We are honored to have as our witness today Mr. Olav J. Braenden, the distinguished Norwegian scientist who is the head of the United Nations Narcotics Laboratory in Geneva for the past 14 years. We decided to invite your testimony, Dr. Braenden, on the recommendation of Gen. Lewis W. Walt who, as you know, has been directing a study of the world drug traffic for the subcommittee. There has been a great deal of confusion in our country on the subject of marihuana and what to do about it, and it was General Walt's conviction that your scientific experience, especially in the field of cannabis research, would help us to make up our minds. It was also General Walt's conviction that the problem of heroin cannot be considered in isolation from the problem posed by the spreading use of other drugs, including marihuana.

Doctor, do you have a prepared statement?

Dr. BRAENDEN. Yes, I have.

The CHAIRMAN. You may proceed.

## STATEMENT OF DR. OLAV J. BRAENDEN, DIRECTOR, UNITED NATIONS NARCOTICS LABORATORY, GENEVA, SWITZERLAND

Dr. BRAENDEN. Mr. Chairman, it is an honor to be called to appear as a scientific witness before this important and distinguished committee. My terms of reference are, as I understand them, to report on certain significant aspects of research on cannabis—of which marihuana and hashish are the chief products—and on the findings of the United Nations Laboratory and of national scientists collaborating with it in the U.N. research program. After giving you a brief outline of recent important developments in the field of cannabis research, I shall, of course, be pleased to answer as far as I can any questions which the members of this committee may care to put to me.

Just before leaving Geneva, I made telephone calls to a number of scientists in different countries who have been collaborating on various aspects of cannabis research. I had lengthy conversations with Prof. W. D. M. Paton of Oxford University, with Dr. Ole Rafaelsen of Denmark, with Prof. C. Miras of the University of Athens, and with Prof. Cornelius Salamink of the University of Utrecht in the Netherlands. The statement I have prepared refers to some of the recent scientific findings on the subject and, I believe, accurately reflects their views, so far as their own research is concerned.

As you know, careful and profound chemical and pharmacological studies of cannabis have also been carried out in this country, particularly under the auspices of the National Institute of Mental Health, The many outstanding scientists who have worked on these studies include Prof. Harry Isbell, Prof. Leo Hollister, Prof. Coy Waller, Dr. Julius Axelrod, Dr. Glenn Kipplinger, and others. Their research, in general, corroborates the research of the European scientists working on cannabis. I regret that there was no time to interview these outstanding scientists before my appearance.

Among the scientists working in the field, it would seem that there is a general consensus that cannabis is dangerous—opinions differ, however, on the degree of the danger to the individual and to society. In my opinion, it seems that, as progressively more scientific facts are discovered about cannabis, the more one becomes aware of its potential dangers.

In spite of the intensive research carried out in many countries, much remains to be elucidated in connection with the chemistry of the components of cannabis and their effects on the body. There is no doubt that this is a highly complex field, much more so than was previously supposed. For example, it had been believed for some decades that the main components of cannabis were some few substances, mainly cannabinoids, of which only tetrahydrocannabinol, or THC as we call it, was the active principle. However, there is now evidence that cannabis contains a very large number of substances—at least 50. The great majority of these components have not yet been isolated and characterized, and their pharmacological activity—or inactivity—remains to be determined.

In our laboratory, we have recently found indications of the presence in cannabis of nitrogen-containing substances. By varying the classical extraction procedures, certain spots were obtained on thin-layer chromatograms which led us to suspect that cannabis contained components of an alkaloidal nature. It was also noted that these alkaloidal substances were present in greater amounts in the actual plant material than in the resin.

The CHAIRMAN. Could you give us a simple definition of an alkaloidal substance?

Dr. BRAENDEN. Well, that is a common term for an alkali containing plant, substances. There are a number of such substances found in nature, and they usually have other specific and strong activities on the human body. For instance, as an alkaloid I can mention nicotine.

The CHAIRMAN. Well, morphine or heroin then is an alkaloid?

Dr. BRAENDEN. Can I answer?

The CHAIRMAN. Proceed. Yes.

Dr. BRAENDEN. The heroin, strictly speaking, is not an alkaloid because it is not contained in a plant. It is a derivative of an alkaloid. It is a derivative of morphine. But people call it an alkaloid, so you are perfectly right, Senator.

The CHAIRMAN. Proceed.

Dr. BRAENDEN. Application of the usual tests for alkaloids was found by Dr. H. Samrah, of Egypt, to give positive reactions. Similar results were obtained by Prof. O. Aguar, of the University of Madrid. These alkaloidal substances have still to be isolated and characterized. Simultaneously and independently, Prof. C. Salemink, of the University of Utrecht, reported on quarternary nitrogen bases in cannabis seeds, and, very recently, on the presence of indole compounds in cannabis itself. (Indole compounds are also nitrogen-containing organic compounds.)

There is no doubt that the presence of nitrogen-containing compounds in cannabis opens a highly interesting field in connection with the pharmacological activity of cannabis because as I said, such plant substances are frequently active.

Mr. SOURWINE. You mean by active that they are poisonous?

Dr. BRAENDEN. Poisonous and active; yes.

Knowledge of the short- and long-term effects of cannabis is far from comprehensive.

According to Dr. A. M. Campbell and his colleagues, of the Bristol Royal United Hospital, there is significant evidence of cerebral atrophy in young cannabis smokers.

Prof. C. Miras, of the University of Athens, has done considerable research on the effects of cannabis on man. As subjects he uses chronic hashish smokers only—because he believes that there is a great risk of damage if the subjects have not previously taken hashish on a regular basis.

The CHAIRMAN. What does hashish do to a person?

Dr. BRAENDEN. What hashish does? Excuse me, Senator.

The CHAIRMAN. What does hashish do to the person?

Dr. BRAENDEN. Senator, this is, of course, a question which is somewhat outside my competence. But, I always used to refer myself, when I get that question, to a report, the report of the Department of Health, Education, and Welfare of the United States to the Congress. So, you certainly have this document, and outside of that I would not, could not make any better statement than what is there. This is as comprehensive as you can get.

Do you want me to read from it?

The CHAIRMAN. No, sir. That is all right. It will be made a part of the record by reference. Proceed, sir.

Dr. BRAENDEN. Dr. O. Rafaelsen, of the Central State Hospital of Copenhagen, Denmark, has found that there is considerable impairment of driving ability after oral ingestion of cannabis.

Here it should be noted that the effects of cannabis when smoked are considerably greater than when cannabis is taken orally. This may be due to the fact that—as reported by Professor Salemink, of the Netherlands—the components of cannabis may in part be destroyed in the digestive tract by intestinal bacteria.

A complicating factor in assessing reports on the abuse of cannabis, particularly by young people, is that those who claim to have smoked

cannabis may not, in fact, have done so—because cannabis in the illicit drug traffic is often highly adulterated with tobacco and other substances, and sometimes it is even completely falsified. In the illicit traffic, it has been reported that a considerable percentage of the samples seized did not contain any cannabis.

As I have pointed out, the activity of cannabis has thus far been attributed entirely to the tetrahydrocannabinol, or THC, which it contains. While it is true that THC is active pharmacologically, it is highly probable that other components of cannabis may also be active. In the Netherlands, a sample of cannabis was found to be highly active despite the fact that no THC was present.

Although an adequate picture of the fate of cannabis in the body remains to be determined, it should be noted that cannabis is only partially excreted by the organism. Professor Paton of Oxford University has found that some of its components accumulate in the fatty tissues of the body.

For a number of years now, the United Nations Laboratory has been engaged in research on cannabis. Acting on a directive of the UN Commission on Narcotic Drugs, we have, in fact, accorded this work the highest priority. Governments have indicated their interest by providing large numbers of cannabis samples for our research, and also by nominating national scientists to participate in the program. These scientists performing their research on a voluntary basis have made important contributions to the program.

Mr. SOURWINE. Mr. Chairman, may I interrupt here, please.

Senator GURNEY (presiding). Yes.

Mr. SOURWINE. Doctor, I want to go back to your previous paragraph. I have been thinking about it since you said it, that some of the components of THC or cannabis, at least, accumulate in the fatty tissues of the body. Is that a parallel phenomena with what we find in DDT, which we are now coming to learn accumulates in the body, and gradually builds up until it eventually, they say, will reach a lethal dose? Is this same thing happening with cannabis smokers?

Dr. BRAENDEN. Yes; Senator. I would be inclined to think so. It accumulates according to the way that you use it.

Mr. SOURWINE. Doctor, I am not a Senator. The chairman is a Senator, and I am the committee counsel. Thank you for your reply.

Dr. BRAENDEN. Shall I go on?

Senator GURNEY. Go ahead and proceed.

Dr. BRAENDEN. The United Nations Laboratory concentrates its attention on those aspects of the research which cannot easily be carried out by national laboratories and, in this connection, its most important function is to coordinate, as required and as far as possible, the research being carried out in various countries within the framework of the program. In particular, we seek to avoid unnecessary duplication of effort. The Laboratory cooperates with researchers in the United States of America, through the National Institute of Mental Health, and it also is in close contact with the Laboratory Division of the Bureau of Narcotics and Dangerous Drugs. In the research program, the laboratory provides its national collaborating scientists with the basic research materials—samples of cannabis, cannabis resin, and cannabis seeds, and it also distributes THC which has been made available through the National Intitute of Mental Health.

Senator GURNEY. Doctor, can you explain in a little more detail how your research differs from that done by the national laboratories of various countries?

Dr. BRAENDEN. Senator, our research is more of a coordinating nature. We do not have the stuff to go deep into the investigations ourselves. We do not have, for instance, animals for pharmacological testing, so this is done by national laboratories. We provide material to these national laboratories which we receive from governments and from institutions.

Does that answer your question?

Senator GURNEY. Yes. Go ahead.

Dr. BRAENDEN. It is well known that the chemical composition of cannabis varies according to the ecological conditions of the region where it is grown, and that, after harvesting, changes occur with time and according to the conditions of storage. The Laboratory has, therefore, organized an ecological study of the variations in the amount and potency of cannabis resin according to ecological conditions. For this purpose, cannabis seeds from the same batches are being cultivated under carefully controlled conditions in various climatic regions. The preliminary studies have yielded some highly interesting results. It has, for instance, been found that the cannabis cultivated experimentally in Iceland and Norway, north of the Polar Circle, from seeds of South African origin, contains appreciable amounts of THC. These findings contradict the previously held belief that cannabis grown in temperate or cold regions is not pharmocologically active. It is our hope that this ecological study will be completed toward the end of next year.

The systematic analysis at regular intervals of the samples of cannabis in the United Nations collection is now being undertaken in order to determine the nature and the extent of changes occurring in composition with time.

The variations in the chemical results obtained in early research on cannabis were probably due, at least in part, to the variations in the cannabis samples used by different scientists. To overcome this difficulty, the United Nations Laboratory has, from time to time, prepared reference samples of cannabis to be used for comparative purposes.

It may perhaps be of interest to mention that, in the illicit traffic, cannabis is now being encountered in a new form—known as "liquid hashish" or "marihuana oil." This is many times as potent as good grade hashish and is potentially very dangerous. The exact technique for producing liquid hashish is not known, but, according to the Bureau of Narcotics and Dangerous Drugs, the hashish is apparently extracted with an organic solvent which is subsequently evaporated, and a vegetable oil is added to the residue. Earlier this year, our Laboratory received interesting samples of some "liquid hashish" or "marihuana oil" seized in Norway. It was said to be of Middle Asian origin, and it had an extraordinarily high concentration or THC—66.3 percent, as against about 10 percent in ordinary hashish and 2 percent in marihuana.

Senator GURNEY. What is the significance of this? Is the high concentration of THC fatal to somebody using it?

Dr. BRAENDEN. Yes. The danger increases with the concentration, of course. The reason for this being done is that they can make the volume so much smaller and hide it so much easier. This is the object of it.

Senator GURNEY. What are the effects of THC on a person?

Dr. BRAENDEN. Would you repeat that, sir?

Senator GURNEY. What are the effects of THC on a user's body?

Dr. BRAENDEN. The effects of THC are very similar to that of cannabis. It was thought before to be the active principle of cannabis, so that really you would get the same effects for THC as you get from cannabis.

Senator GURNEY. All right. Proceed.

Dr. BRAENDEN. In spite of the progress made in recent years, in cannabis research, much still remains to be done before we have an adequate understanding of the nature and effects of this complex plant. Very considerable research is necessary—particularly in order to isolate and characterize all the relevant constituents of cannabis; to definitely establish the active principles; to study the pharmacological effects of cannabis and its fate in the body; and also to determine the chemical transformations which occur in cannabis when it is smoked.

I feel, therefore, Mr. Chairman, that every effort should be made to accelerate relevant research so that it may be possible, within the near future, to draw sound scientifically based conclusions on cannabis—conclusions which would be of value to national and international bodies in their considerations of the control of cannabis.

Thank you, Mr. Chairman.

Senator GURNEY. Well, thank you for your statement, Doctor.

The Shafer Commission, in its report, listed a number of different countries for gathering of material. Did they visit the United Nations Narcotics Laboratory in Geneva?

Dr. BRAENDEN. I must say that we have quite a number of committees visiting us. When you mention the Shafer Commission, I do not recollect that name, and as I can see, it is not mentioned in the Shafer Report, so I suppose that they have not been there. But, it could also happen that I have been on leave at the time when they visited us.

Senator GURNEY. At any rate, no one from that Commission talked to you?

Dr. BRAENDEN. No. No. That is what I said, I do not remember it.

Senator GURNEY. Had they sought your views, would your views be the same as you have presented to the committee here today?

Dr. BRAENDEN. Well, Mr. Chairman, I am not quite sure when this study was made. I suppose that was a year ago, was it not?

Senator GURNEY. Do you recall when that study was made?

Mr. SOURWINE. Yes, sir, about a year ago, Mr. Chairman.

Senator GURNEY. Yes, about a year ago.

Dr. BRAENDEN. You know, at that time, it was not possible to give the information that I have given to you from Copenhagen, from the tests at Athens, and London, as I have given them to you now, because they are very recent, the results.

Senator GURNEY. Is it a fair thing to say from your statement that you consider cannabis to be a dangerous substance?

Dr. BRAENDEN. Yes, it is. I do not think there is anybody who questions that cannabis is dangerous. The question is the degree of dangerousness, and this is what the research is needed for, in order to find out.

Senator GURNEY. Would you be in favor of legalizing the use of marihuana?

Dr. BRAENDEN. This is a legal question which I am not authorized to answer. For this you would have to ask a legal expert, and you certainly are in a better position to judge the situation yourself. The only thing which I can do is to bring to your attention the scientific facts as they are today, and what we hope, and what research we hope to do in order to clarify the situation.

Senator GURNEY. Well, let me put the question the other way. Forgetting or putting aside your official capacity as head of the United Nations Narcotics Laboratory, would you personally, as an individual, not in your position, but as an individual, favor the legalization of marihuana?

Dr. BRAENDEN. I would say well, generally, I would say that it is better to be careful when it comes to medicine and drug policy than it is to be careless. I think that you people here in the United States have an excellent example of this in the thalidimide case, which you did not authorize for use before you wanted more research done, and that saved you from some 10,000 malformed children as they have in Europe from this case.

Senator GURNEY. And then I think it would be, as I understand your testimony. and your answers to the questions, it would be your view that not enough is known about marihuana to make a judgment as to whether its use should be legalized now or not, is that right?

Dr. BRAENDEN. Well, this would be my feeling, yes, that much more research should be done so as to be able to take the right position in establishing controls over marihuana.

Senator GURNEY. A great many statements are made these days on marihuana in which they say that this really is very little different than the use of alcohol or tobacco or marihuana, that all of these substances are harmful if you indulge too much in any one of them, and there really is little choice between them. One is not any more dangerous than the other. Of course, this is the argument which is made by the marihuana users—that marihuana ought to be legalized because it really is not any more harmful than heavy use of tobacco or alcohol. What is your view on that?

Dr. BRAENDEN. I think there is a substantial difference between cannabis and alcohol in that alcohol is readily excreted from the body. It is not accumulated, as I mentioned, is the case with the cannabis. I think this is one of the rather substantial differences which has to be taken into consideration.

Mr. SOURWINE. Is nicotine also secreted, or does it accumulate in the tissue?

Dr. BRAENDEN. That does not accumulate either, as far as I know.

Senator GURNEY. I see. We have a vote on the floor now, so the subcommittee will recess temporarily subject to the call of the Chair.

(Short break.)

Senator GURNEY. The subcommittee will come to order.

Doctor, it is our understanding that the United Nations Laboratory, of which you are the head, has developed procedures for identifying opium by geographic origin. Could you explain how this was done?

Dr. BRAENDEN. Yes. I could have explained it better if we had a projector, but I will try to explain it otherwise. It is in a way the same principle as identifying a fingerprint in that, you see, the opium is a

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plant material, and this differs according to the growing condition. You know, like coffee from Java is different than coffee from Brazil. And there are a lot of examples like this.

Now, in the case of opium, it is, it develops a difference in the quantity of the various substances there, mainly the alkaloids of opium, and it is then measured on a spectrophotometric. It is kind of a pattern of curves, and really this is what you have in fingerprints, too, you have a pattern of curves.

Mr. SOURWINE. Is this a spectrographic process?

Dr. BRAENDEN. Spectrophotometric, not spectrographic. Spectrographic would be more concerned with the metal components of opium.

Mr. SOURWINE. Not spectrographics, but spectro what?

Dr. BRAENDEN. Spectrophotometric or colormetric, we call it also.

Mr. SOURWINE. Colormetric?

Dr. BRAENDEN. Colormetric, the intensity of the color.

Mr. SOURWINE. Would it be true then, I will try to ask a layman's question so that whoever reads this will understand, in a sense you are taking a picture of the differences, the peculiarities and the individualities of a specimen?

Dr. BRAENDEN. That is right.

Mr. SOURWINE. Which shows up interaction or variation in color or in position, and which is unique to the particular specimen?

Dr. BRAENDEN. This is about right, yes.

Mr. SOURWINE. So that once you have this picture, you do not need another specimen in order to compare? The picture identifies that specimen for all time?

Dr. BRAENDEN. That is probably not so.

Mr. SOURWINE. Not so?

Dr BRAENDEN. One has to check from time to time and get new samples from the region. We do not have enough information on this to answer this question. As a matter of fact, that work was rather important about 10 years ago. Now it is less important because the opium travels much shorter distances. It is transferred into heroin or transferred into morphine or into heroin very near to the production of the opium because this is much easier to transport. But, it could, it could have very interesting application in some regions. For instance, in Southeast Asia, where there is still quite a lot of opium seized from Thailand, Burma area, the Laos area and so on, it may be that in that part, one could, by your method, trace back to the origin, and this could be very useful.

Mr. SOURWINE. Doctor, I will ask you to identify for the record three documents which you were good enough to furnish for the use of the subcommittee. They bear the imprint of the United Nations Secretariat, and they all bear the general caption "the assay, characteristics, composition and origin of opium." The first document is No. 82 and bears the subtitle "List of authenticated samples in the United Nations distribution center." The second document is No. 87 and bears the subtitle "Determination of the origin of opium by direct absorption spectrophotometry," and the third document, No. 104, bears the subtitle "Study on the microscopic appearance and classification of opium samples from different countries." I simply ask if you can identify these three documents as documents issued by the U.N. Secretariat?

Dr. BRAENDEN. Yes, that is right, sir.

Mr. SOURWINE. They were prepared by your laboratory?

Dr. BRAENDEN. It was prepared.

Mr. SOURWINE. Mr. Chairman, I ask that these go in the appendix of the record, not for complete reproduction, but for the records to be in the committee file.

The CHAIRMAN. That will be so included.

(The three documents referred to may be found in the files of the subcommittee.)

Mr. SOURWINE. I have one more thing, Doctor. I show you a statistical breakdown by country of origin of authenticated samples of opium in the United Nations Laboratory, and I ask if this breakdown was prepared by your laboratory?

Dr. BRAENDEN. Yes; this was prepared by our laboratory. Yes.

Mr. SOURWINE. May this go in the record at this point?

Senator GURNEY. It will be included in the record at this point.

*Authenticated samples of opium received by the United Nations Laboratory*

| | |
|---|---|
| Afghanistan (presumably samples from illicit production) | 3 |
| Burma (including authenticated samples of illicit production) | 4 |
| China (this sample, consisting of 4 lumps, was received in 1951) | 1 |
| Greece (from Macedonia before the cessation of opium production in Greece) | 1 |
| India | 620 |
| Indochina region (apparently from the region which subsequently became Laos) | 2 |
| Iran (mostly from production before the temporary ban on the cultivation of the opium poppy) | 48 |
| Japan | 27 |
| Laos (prepared opium) | 3 |
| Mexico (including samples of illicit production) | 5 |
| Nepal | 1 |
| Pakistan | 13 |
| Republic of Korea (including authenticated samples of illicit production) | 4 |
| Thailand | 3 |
| Turkey (mostly from districts where opium production has now ceased) | 87 |
| Union of Soviet Socialist Republics | 18 |
| Viet-Nam | 1 |
| Yugoslavia | 11 |

Mr. SOURWINE. Doctor, I would like to ask you this: from what you have already said, I take it that you must have a fair number of samples from each country that produces opium in order to make the procedure of identification reasonably accurate?

Dr. BRAENDEN. Yes; that is right.

Mr. SOURWINE. I note from this list, your authenticated samples list, that has just gone in the record that, for instance, you have 620 samples from India, 87 from Turkey, 48 from Iran, 18 from the Soviet Union, but only one from Vietnam and only one from China. One sample is really not enough to make serious identification possible?

Dr. BRAENDEN. No.

Mr. SOURWINE. Would it be posible to determine the geographic origin of morphine base by a similiar procedure?

Dr. BRAENDEN. No; it would not, but one could do some work in that direction by linking the, well, the samples together. It would be the same situation with counterfeit money, where we would know where the samples turned up, but we would not know where it was made. But, also, this would be the same thing as with counterfeit money where you know where the money turns up, but you do not know where the press is.

Mr. SOURWINE. Understood. Would it be possible to determine the geographic origin of the opium from which a specific batch of heroin has been defined?

Dr. BRAENDEN. No. This would be even more difficult.

Mr. SOURWINE. I have no more questions, Mr. Chairman, except perhaps I should ask this catchall. Doctor, is there any other aspect of your current narcotics research that you would tell us about?

Dr. BRAENDEN. There is one aspect which could be of interest to you. That is the question of *Papaver bracteatum*, and this is the question of poppy thebaine. This is a poppy which grows wild in Iran, in the mountains north of Iran, and it contains thebaine, appreciable amounts of thebaine, but no morphine. Now, thebaine can be trasferred into codein, and codein is really what is used of the opium poppy. And 90 percent of the morphine which is produced in the world is transfered to codein. So, if this plant, if it really is what it looks like, and if it would be economical, this would probably lead to a cutting down of the leading production of opium to one-tenth of what it is now, and still the requirements of the country could be met. Thebaine is not an addictive.

Mr. SOURWINE. You say there is a kind of poppy that would produce codein but would not produce opium, or at least would produce only a small amount of opium?

Dr. BRAENDEN. No, it is not quite like that. It produces a substance which one can use for making codein but it does not produce morphine or any other addiction-producing substance.

Mr. SOURWINE. I understand, sir.

Dr. BRAENDEN. So, this is really an interesting field, and we have now in cooperation with the Department of Agriculture of the United States, we have planted this, the seeds of this plant in various parts of the world, in Scandinavia, in Turkey, and also over in Thailand. And it is going to be produced now, or cultivated. This could give the farmers a cash crop, I mean the opium farmers a cash crop without changing too much their way of cultivation, because this will also be a poppy, you see.

Thank you, Mr. Chairman.

Senator GURNEY. Well, thank you, Dr. Braenden. You have shed a lot of light on the very troublesome subject of drugs, and it is a world-wide problem, of course, now. We appreciate very much your coming here this morning before the subcommittee and giving us the benefit of your knowledge. Thank you.

Mr. SOURWINE. Mr. Chairman, these other witnesses were scheduled to testify. They are Eugene T. Rossides, John E. Ingersoll, and Nelson Gross. We have their statements, which should be made part of the record. May they be ordered printed as though read?

Senator GURNEY. So ordered.

(Because of the length of the above mentioned, the statements of Messrs. Rossides, Ingersoll, and Gross were ordered printed in a separate volume.)

The subcommittee will recess, subject to the call of the Chair.

(Whereupon, at 11:55 a.m., the hearing was recessed, subject to the call of the Chair.)

(Seven articles dealing with the injurious effects of cannabis were subsequently ordered into the record. Because the articles are lengthy and technical, each is preceded by an editorial summary.)

# APPENDIX

[From Drugs and Society, Jan. 9, 1972, pp. 17–20]

GUIDE TO DRUGS

(By Prof. W. D. Paton)

*Editorial summary*

1. "Little is known about the composition of the smoke from cannabis cigarettes, save that about 25 to 50 percent of the THC content is delivered to the respiratory tract."

2. "The cannabinoids are extremely fat-soluble and correspondingly insoluable in water. They and their metabolites therefore persist in the body; thus, 24 hours after a dose of labelled THC a rat has eliminated, as metabolites in urine and feces, about 10 percent of the dose, a rabbit about 45 percent and a man about 25 percent."

3. "Cannabis has not been found to produce fetal deformities and fetal resorption in animals (rats, rabbits and hamsters) in doses (per unit or bodyweight) ranging down to that used in man. The effect has been shown to be dose-related . . . and is exerted at all small fraction of the dose liable to kill the mother." In this respect it resembles Thalidomide and other human teratogens. [A teratogen is a substance which causes fetal deformities.]

4. Although only a small proportion of casual cannabis users progress to heroin or other opiates, progression is much commoner with heavy users, while the vast majority of opiate users have had prior experience with cannabis. The progression can be explained pharmacologically by the fact that cannabis increases suggestibility, and shares with heroin (although in milder form) the ability to produce euphoria and analgesia.

5. "There seems no rational basis for drawing a line between cannabis on the one hand and LSD, the amphetamines or the potent opiates, on the other."

*Cannabis sativa* is a widely distributed plant producing fibre oil (from its seeds) and resin in varying proportions according to its variety and the conditions of cultivation. The resin is produced mainly in the flowering tops. Marijuana, made from the dried plant, contains a good deal of other plant material mixed with the resin; in hashish the resin is more or less concentrated. The term 'cannabis' will be used to refer to any preparation of the crude material.

BIOCHEMISTRY OF CANNABIS

Cannabis differs from the other drugs discussed in this series in always being a mixture of substances. Of the scores of chemical compounds that the resin contains, the most important are the oily cannabinoids, including tetrahydrocannabinol (THC), which is the chief cause of the psychic action. Samples of resin vary greatly in the amounts and proportions of these cannabinoids according to their country of origin; and as the sample ages, its THC content declines.

As a result, the THC content of samples can vary from almost zero to eight per cent. Pure THC is unstable unless kept in the dark under nitrogen, but is better preserved in the undamaged plant. One result of these facts is that the dose of THC taken, unless under laboratory control, is far more uncertain than with other drugs.

In addition to the cannabinoids are certain water-soluble substances, including a small amount of an atropine-like substance (which may contribute to the dry mouth), and some acetylcholine-like substances (which may contribute to the irritant effect of the smoke).

Little is known about the composition of the smoke from a cannabis cigarette, save that about twenty five to fifty percent of the THC content is delivered to the respiratory tract.

THC and other cannabinoids are now fairly easily detectable in small amounts by gas-liquid chromatography. But once THC enters the body, it is hard to trace, unless it has been labelled for research purposes with a radioactive atom—partly because it is taken up by the tissues, partly because it undergoes a series of still incompletely understood conversions. The products of these conversions are found in the urine, but a urine or blood test suitable for forensic or research use is still not available. This is a serious handicap to clinical investigation and means, that there is no way of establishing how much (if any) cannabis a subject has taken.

The cannabinoids are extremely fat-soluble, and correspondingly insoluble in water. They and their metabolites therefore persist in the body; thus twenty four hours after a dose of labelled THC, a rat has eliminated, as metabolites in urine and feces, about 10 per cent of the dose, a rabbit about forty five per cent, and a man about twenty five per cent.

### PSYCHIC EFFECTS

Reactions are very varied, and they are much influenced by the behavior of the group. Euphoria is common, though not invariable, with giggling or laughter which can seem pointless to an observer. Sensations become more vivid, especially visual, and contrast and intensity of color can increase, although no change in acidity occurs. Size of objects and distance are distorted. Time as experienced becomes longer than clock time; thus a subject asked to say when sixty seconds has elapsed responds too early, but if asked to say how long some period of time was, overstates it; sense of time can disappear altogether, leaving a sometimes distressing sense of timelessness. Recent memory and selective attention are impaired; the beginning of a sentence may be forgotten before it is finished, and the subject is very suggestible and easily distracted. Psychological tests such as mental arithmetic, digit-symbol substitution, and pursuit meter tests show impairment, the effect being greater as the task becomes more complex. The vividness of sensory impressions and distractibility gives rise to imagery and fantasy; this can progress with increasing dose from mere fanciful interpretation of actual sensations to hallucination in the sense of vivid sensory impressions lacking an external basis. These effects may be accompanied by feelings of deep insight and truth. They are similar in type, though often more intense, to those experienced in hypnagogic imagery or while recovering from an anaesthetic.

It seems likely that these effects of cannabis can be explained if it removes a restraining 'gate' on the inflow of sensory information. Normally, considerable selection takes place, and familiar stimuli or those judged irrelevant are ignored. A dis-inhibitory action of cannabis, lifting this gate, would allow the 'flood of sensation' so often reported. Further, it is believed that time sense depends on the frequency of sensory impressions; an increased flow would therefore give the feeling that more time had elapsed. Finally, it is known that the process of memory involves at least three processes: entry into a sensory 'register' and passage into a short-term 'store'; rehearsal of information either consciously or unconsciously, leading to consolidation and transfer to a longer-term store; and retrieval. It appears that retrieval is not impaired by cannabis (longstanding memories often form the basis of the imagery), and entry seems normal; but conversion of short-term to long-term memory is known to be interfered with by a flow of additional sensory impressions, just as a telephone number is likely to be forgotten if someone speaks to you just after you have heard it. It is likely that the flow of sensory impressions under cannabis interferes with the consolidation of recent information in a similar way. Once memory is impaired, concentration becomes less effective, since the object of attention is less well remembered. With this may go an insensitivity to danger or the consequences of actions.

A striking phenomenon is the intermittent wave-like nature of these effects—a subject may return towards normal, or bring himself 'down' for a period. This intermittance effects mood, visual impressions, time sense, spatial sense, and other functions: it represents, incidentally, one of the many experimental difficulties in analyzing cannabis action. The effect of a single dose usually ends with drowsiness or actual sleep.

The effects can also be unpleasant, especially by inexperienced subjects, particularly timelessness and the feeling of loss of control of mental processes. Feelings of unease, sometimes amounting to anguish, occur, and may well have some physical basis—perhaps associated with the acceleration of the heart rate. There is also, especially in the habitual user, a tendency to paranoid thinking. High or habitual use can be followed by a psychotic state; this is usually reversible, quickly with brief periods of cannabis use, but more slowly after sustained exposures.

PHYSIOLOGY

Cannabis smoked or taken by mouth produces reddening of the eyeballs (probably the forerunner of the general dilation of blood vessels and fall of blood pressure with higher doses), unsteadiness (particularly for precise movements), and acceleration of heart rate. The latter effect can be substantial, and although the insolubility of the cannabinoids in water makes intravenous abuse difficult, cardiac failure would be a serious risk with such use. The smoke produces the usual smoker's cough, and the tar from reefer cigarettes is as carcinogenic in animal experiments as cigarette tobacco tar. Although increase in appetite is commonly experienced, no explanation for it exists, and cannabis use does not have any striking effect on the blood sugar. In animals, with chronic administration of substantial doses, food intake is reduced and weight loss occurs.

An important finding in animals is that cannabis prolongs sleeping time after a dose of a barbiturate such as pentobarbitone (Nembutal). This has been shown to be due to an impairment of the ability of the liver to break down (metabolise) the barbiturate, as a result of inhibition of the microsomal enzymes. The importance lies in the fact that many drugs used in medicine are also dealt with by these enzymes; and it is to be expected that their functions will be impaired in the case of any recent or habitual cannabis user. The effect is not due to THC itself, but mainly to another constituent of the resin, cannabidiol. One hopes that cannabis users seeking medical treatment would inform their doctors accordingly the main danger would be of overdosage or of overprolonged action.

A recent report has concerned the loss of brain substance, as measured by the technique of air encephalography, in a group of ten young heavy cannabis users. The enlargement of the ventricles of the brain is of the type that occurs in old age, or in middle years with chronic alcoholics. The work needs confirmation, since although the subjects had taken hundreds of doses of cannabis, they also had a number of doses of LSD or amphetamines, and occasionally heroin. One is, however, bound to take it seriously, since cannabis, the main drug used by the patients, is cumulative, with a very high affinity for fat, and able to impair cell division by lymphocytes in tissue culture.

Cannabis has been found to produce fetal deformities and fetal resorption in animals (rats, rabbits and hamsters) in doses (per unit weight) ranging down to that used in man. The effect has been shown to be dose-related, and (unlike the teratogenic effect in animals of many drugs, but like thalidomide and other known human teratogens) is exerted at a small fraction of the dose liable to kill the mother. It is not clear what the effect in the human is, and it is to be hoped that it is the human equivalent of fetal resorption (miscarriage) rather than teratogenicity. Tests for chromosome damage have been negative, so that there is no evidence for a heritable genetic defect; but the same tests showed an impairment of cell division, and it may well be this, applied to the developing fetus, which causes the reduction deformities. The teratogenic effects appear to be due to some factor other than THC in the resin.

CANNABIS AND CRIME

There is much debate about the connection between cannabis and criminality. A reasonable view, covering other aspects of behavior, is that cannabis may accentuate a particular mood or facilitate a train of action and such a process could well explain the case of violence described. A similar position could hold about the connection with sexual behavior. But here two other contrasting factors enter; the alteration in time sense would change the apparent duration of sexual inter-

course; and the predisposition to fantasy may replace actual activity with images of it. There is, too, the unexplored possibility that the circulatory effects of cannabis include a mild genital engorgement.

More important, however, is likely to be the effect of repeated use described as the "amotivational syndrome". This term dignifies a still imprecisely characterized state, ranging from a feeling of unease and sense of not being fully effective, up to a gross lethargy, with social passivity and deterioration. It is difficult to assess, when personal traits and intellectual rejection of technological civilization are also taken into account. Yet the reversibility of the state, its association with cannabis use, and its recognition by cannabis users make it impossible to ignore.

ESCALATION THEORY

Attention has mainly concentrated on progression from cannabis to heroin or other opiates. Although only a very small proportion of casual users progress, it is much commoner with heavy users, and the vast majority of opiate users have prior experience of cannabis. Although it is often said that there is no pharmacological basis for such progression, this in fact exists, since cannabis increases suggestibility and shares with heroin (though in milder form) the ability to produce euphoria and analgesia.

But the situation is a more general one. It seems probable that amphetamine use also predisposes to heroin use; and the overlap in actions between cannabis and LSD makes intelligible the observed progression to LSD. The role of prior use of "soft" drugs, or use of drugs by "soft" techniques in predisposing to more serious abuse needs much more study, particularly by methods which can establish objectively the actual amount of drug used. Although it can only be one of many factors, it could be important in the prevention of serious abuse.

TOLERANCE AND DEPENDENCE

Tolerance to the behavioral effects of cannabis and of THC in animals has now been repeatedly demonstrated. As with the fat-soluble barbiturates, the first few doses may cumulate, masking the underlying development of insensitivity to the drug's effects. It is not clear whether the tolerance results from increased destruction of the drug or a resistance at the cellular level.

In man, the evidence is largely and anecdotal and uncontrolled (this applies to Weil and Zinberg's data, since the experimental subjects but not the naive were told what they were to receive). There is limited evidence that THC disappears somewhat faster from the blood users as compared with naive subjects. Perhaps the best evidence is still that in the Laguardia report, where it was found that a three times higher dose was required to produce a given degree of ataxia in users than in non-users. Withdrawal symptoms of morphine or barbiturate type do not occur: but after heavy use, depression, anxiety, sleep disturbance, tremor and other symptoms develop, and many users find it very difficult to abandon cannabis use. In studies on self-administration by monkeys, spontaneous use did not occur, but once use was initiated, drug-seeking behavior developed. Subjects who have become tolerant to LSD or opiates as a result of repeated dosage respond normally to be cross-tolerance between cannabis and alcohol.

IN CONCLUSION

The salient fact about cannabis is that it is a mixture of substances, whose psychically active principle is highly fat-soluble. It seems likely that for the foreseeable future it will be the crude material that is used. The outstanding problem, therefore, is that of the effects of chronic use, not only of THC but of the other constituents. The significance of teratogenesis, of microsomal inhibition, of the amotivational syndrome, and of the observations on brain damage needs clarifying. Hitherto, dependence-liability has rested largely on assertion, but definite evidence should be forthcoming. Methods of measurement of the cannabinoids or their products in blood or urine should also be to hand before too long. One can say, at last, that "work is in progress."

Many general points have been omitted. But three final comments are needed. First, no comparison has been attempted with other drugs such as alcohol which, because of the peculiarities of cannabis, is in any case complicated. But it must be emphasized that such a comparison requires a major effort of the imagination. To estimate the probable result of treating cannabis like alcohol one must suppose it to be as readily available, with equivalent advertisement

and promotion, in an equivalent range of potencies, and used by a comparable proportion of the population. It is peculiarly difficult to extrapolate in this way, given only our knowledge of widespread use of relatively weak crude material in the USA, of less common use of more active material in this country, and poorly characterized endemic use in developing countries. Second, too much stress has been laid on reports such as those by the Indian Hemp Commission: these were relevant to knowledge of the day and the social conditions of a subject country with a low expectation of life, but not to modern conditions in which society and its members expect so much of each other.

Finally, cannabis occupies a fascinating position in the debate of what society should tolerate, and the outcome of the debate will be important. Despite the damage done in later life by alcoholism, it is possible to draw a line between it and cannabis: there seems no rational basis for drawing a line between cannabis on the one hand and LSD, the amphetamines or the less potent opiates on the other.

REFERENCES

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[From the Lancet, Dec. 4, 1971]

CEREBRAL ATROPHY IN YOUNG CANNABIS SMOKERS

A. M. G. Campbell
*Department of Neurology, Bristol Royal United Hospitals*

M. Evans
*Department of Psychiatry, Whitchurch Hospital, Cardiff*

J. L. G. Thomson
*Department of Radiology, Frenchay Hospital, Bristol*

M. J. Williams
*Department of Medicine, Bristol Royal Infirmary*

*Editorial summary*

1. "Personality changes and mental illness have been reported in chronic cannabis smokers over a period of 3–11 years. Addicts often have impairment of recent memory, vegetative symptoms, and a tendency to reversed sleep rhythm suggesting organic brain damage."

2. A study of ten youthful patients with histories of consistent cannabis use over a period of 3–11 years showed serious brain atrophy, comparable to the atrophy that normally takes place between ages 70 and 90.

3. The brains of monkeys given isotope-labelled cannabinols intravenously showed concentration of the drug in the frontal lobes and cortex and other brain sectors near the third and lateral venticles. After 24 hours, the drug had spread uniformly throughout the brain. The fat solubility of the cannabinols make it likely that they would accumulate in the nervous tissues, including the brain, because of their high fat content.

4. Chronic abuse of cannabis and LSD produce symptoms similar to those of *encephalitis lethargica*—an inflammation of the lining of the brain characterized by extreme lethargy. Among these symptoms are, reversal of sleep rhythms, hallucinations, loss of memory, inability to work, and a falling off of moral character.

5. "For many years the production of cerebral atrophy in boxers was not realized. We would suggest that a similar state of affairs is happening in relation to drug abuse. Far too much attention has been paid to psychological and behavioral disturbances without relating these to the possibility of permanent damage to the brain."


## SUMMARY

Evidence of cerebral atrophy was demonstrated by air encephalography in ten patients with histories of consistent cannabis smoking over a period of 3–11 years. The average age of the patients was 22 years; all were males. Amphetamines and lysergide (L.S.D.) had also been taken, but in much smaller amounts. Measurements of the lateral and third ventricles were significantly different from those in thirteen controls of a similar age-group.


## INTRODUCTION

Personality changes and mental illness have been reported in chronic cannabis smokers of previously normal personality [1]. Addicts often have impairment of recent memory [2], vegetative symptoms, and a tendency to reversed sleep rhythm suggesting organic brain damage. If organic brain damage were confirmed, this would clearly lead to a different approach to the problem of increasing drug abuse.

This study was prompted by the finding of cerebral atrophy on air encephalography in four young patients referred to one of us (A. M. G. C.) for neurological investigation of headache, memory loss, or behavior change. A common factor in all four histories was prolonged heavy cannabis smoking. Amphetamines and lysergide (L.S.D.) had also been taken, but in very much smaller amounts. Since no recognized cause of the cerebral atrophy was apparent, neurological and radiological investigation of other cannabis smokers seemed indicated.

## PATIENTS AND METHODS

### *Patients*

The first four cases were unselected routine admission for investigation of neurological symptoms. The next five were under treatment by one of us (M. E.) for drug abuse, and were referred for detailed investigations of cerebral function, including air encephalography. They were selected because of known long-standing cannabis smoking; two had been attending a drug-addiction center for some time and the other three were the next cases which presented to psychiatric outpatients with histories of long-standing cannabis smoking. The tenth patient was admitted as an emergency with a drug overdose and had a 6-year history of drug abuse with heavy cannabis intake. All these cases were given a full clinical examination and were investigated by air encephalography.

It was fully explained to the patients that the test was to assess possible brain damage with a view to ultimate prognosis, and our patients willingly consented to this investigation, which was done under local anesthesia and sedation.

### *Controls*

One of the main difficulties in estimating the size of the cerebral ventricles by air encephalography is the choice of controls. Most published series include patients of all ages; however, the ventricles enlarge with age [3]. The mean age of our patients was 22 years. To obtain normal values for the age range 15–25 years we reviewed the X-ray films and notes of all cases investigated by air encephalography in our neuroradiological unit in which the findings had been reported at the time as normal. We excluded all those with abnormal neurological signs, a raised cerebrospinal-fluid (C.S.F.) protein, or other abnormal features. In this way we obtained thirteen controls; their case-notes indicated that these

had originally been referred because of symptoms such as headache, loss of consciousness, or syncope. Subsequent follow-up on all of these patients had not revealed the development of any neurological illness. A typical control air encephalogram is shown in fig. 1. Particular attention should be paid to the shape of the lateral ventricles anteriorly, especially the sharpness of the lateral and inferior angles and the upward and inward curve of the floor of the body and the posterior part of the frontal horns.

Of the thirteen controls, seven were female and six male. The series of ten drug-taking patients were all male. However, air-encephalograms on the female controls were not significantly different from those of the male controls.

*Radiology*

The standard air-encephalography technique was used in all cases. About 25 ml. of air was injected into the lumbar subarachnoid space with the patient in the sitting position, under basal sedation. Just enough cerebrospinal fluid for routine laboratory testing was removed. Films of the patient's head were taken in this position, and again with the patient supine and prone. Routine views of the temporal horns were also taken. Measurements of the anterior ends of the lateral ventricles were taken from films obtained in the anteroposterior position with the patient supine. Measurements of the lateral ventricular size were carried out using three standard diameters, and an accurate area measurement was also obtained by using a planimeter, an instrument that mechanically integrates a trace of the perimeter of an object into the object. [3] These measurements are illustrated in fig. 2:

"A" is the widest transverse diameter of the frontal horn.

"B" is the oblique diameter from the lateral angle to the junction of the floor of the body of the lateral ventricle with the medial wall.

"C", a line at right angles to B, 5 mm. from its lateral extremity, gives a measure of the lateral angle of the ventricle.

"D" is the transverse diameter of the third ventricle, the posterior width being taken from the film with the patient sitting up, and the anterior width from the film with the patient supine.

"E" is the area of the shadow of the posterior part of the frontal horn of the lateral ventricle (indicated in fig. 2 by the shaded area, and shown in fig. 3 for all cases).

*Other Investigations*

C.S.F. obtained at air encephalography was examined under the microscope and analysed for protein, Wassermann reaction, and Lange curve. The C.S.F. pressure was normal in all cases. Skull and chest X-rays were taken in all cases. Venous blood was tested for hæmoglobin, leucocytecount, erythrocyte-sedimentation rate, urea, electrolytes, and liver function. Results were normal except as stated in cases 1 and 9.

## CASE-REPORTS

*Case 1*

An unemployed steel erector, aged 22, complained of generalized headache over recent months. He had had a probable epileptic fit at age 13 but had not been investigated or treated. It was not known whether he had suffered any birth injury, and there was no family history of epilepsy. At age 18 he was in hospital for 3 days because of a head injury. 3 weeks later he had a grand-mal epileptic attack, with four similar attacks in the next year. The head injury would seem to have exacerbated pre-existing epilepsy.

He had smoked cannabis regularly and frequently since the age of 16. L.S.D. had been taken about twenty times, but he did not admit to taking amphetamine.

On examination he seemed restless, anxious, suspicious, irritable, and despondent. There were no abnormal neurological signs.

Electroencephalography was outside normal limits, displaying minimal features in all areas. There were no focal abnormalities.

At air encephalography diameters A and B were within the normal range, but diameters C were increased and the back ends of the lateral ventricles were somewhat "square" (fig. 4). The third ventricle diameter D was towards the upper limit of normal. The area measurement E was increased on both sides.

*Case 2*

An 18-year-old unemployed salesman was admitted for investigation of change in behavior and impairment of recent memory. He said he was becoming increasingly aggressive and could not understand his own behavior. There had been frequent generalized headache over the previous month. He was an adopted son and his own family history was unknown. At the age of 1 year he had whooping-cough and at 13 he had hepatitis, but neither produced neurological complications.

Drug abuse started when he was 14, amphetamines being passed to him by a fellow choirboy. Within a year he was smoking cannabis regularly and fairly heavily three times a week, and continued to do so. He had taken L.S.D. about twenty times and heroin four times, but discontinued the amphetamines after the first year. He abandoned A-level studies at a technical college and thereafter could only work as a salesman for a short time.

On examination he was excited, exhibited pressure of speech, poor memory, and lack of insight. There were no abnormal physical signs.

At air encephalography diameters A and C (especially C) were increased on both sides. The width of the third ventricle posteriorly was outside normal limits, and the trigone of the left lateral ventricle was rather "square". The area measurement E was also increased on both sides, left more than right (fig. 5).

E.E.G. was normal.

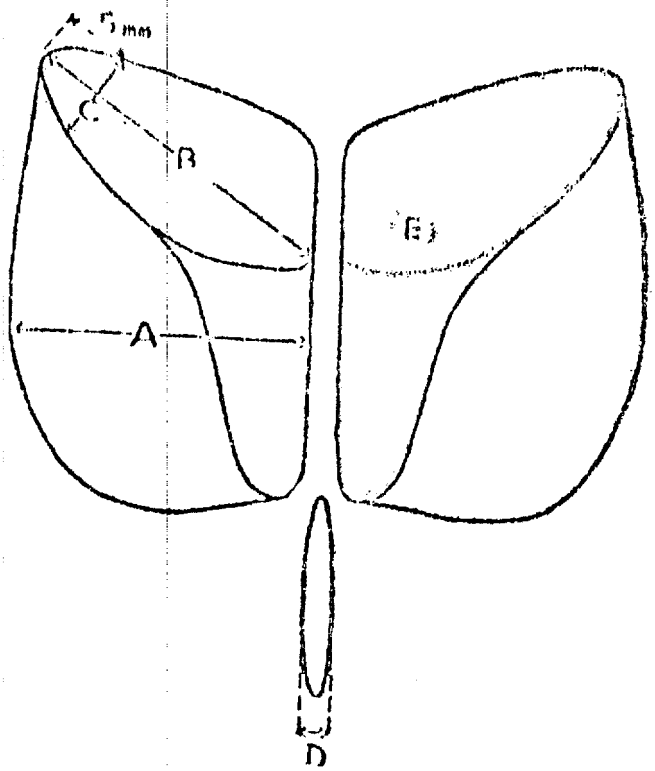


**Fig. 2—Measurements used in assessing ventricular size (see text).**

Areas in sq.cm. shown in table.

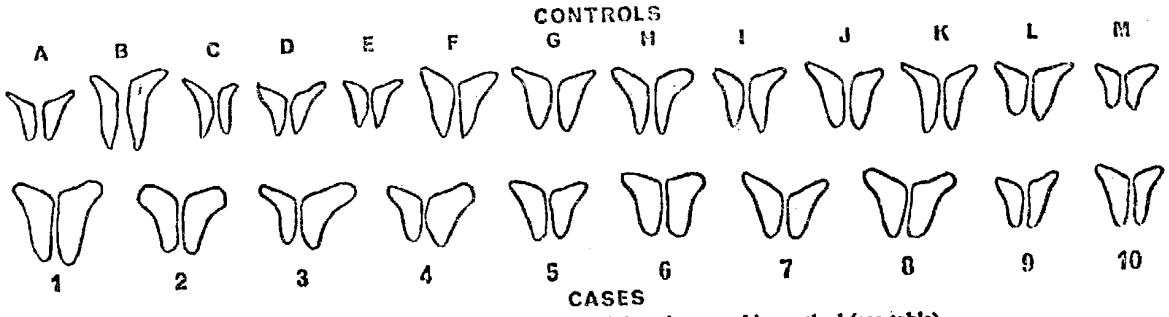


Fig. 3—Outlines of the areas (E) measured by planographic method (see table).

*Case 3*

A 21-year-old computer operator was admitted for investigation of frequent headaches of a year's duration. He also complained of poor concentration. There was no history of birth injury or other significant illness. At age 8 he had had a minor head injury and was unconscious for half-an-hour but did not require hospital admission.

He had smoked cannabis regularly since the age of 15, had taken L.S.D. twice and amphetamines about ten times. Since leaving grammar school he had frequently changed his work, but after his marriage a few months before admission he had stopped taking drugs, and had stayed in the same job.

On examination he was anxious, morose, and withdrawn. He was unable to give a clear account of his symptoms, about which he seemed very concerned. There were no abnormal physical signs.

At air encephalography the diameters A, B, and C of the left lateral ventricle were well outside normal limits (fig. 6). The width of the third ventricle was outside normal limits also, both anteriorly and posteriorly. The trigonal region was "square" on the left side, the left temporal horn dilated, and the surface sulci rather prominent. The area measurement E was increased on the left side.

*Case 4*

An unemployed laborer aged 24, son of an academic, complained of depression and left frontotemporal headaches over the previous 10 months. He also had attacks of photophobia, not necessarily associated with the headache. During the previous year he had twice briefly lost his sense of awareness. He had not fallen, convulsed, or lost consciousness, and witnesses described him as looking vacant for a few moments. There was no significant past illness, but it was not known whether he had suffered any birth injury nor if there was a family history of epilepsy. 3 years previously he had been involved in a motor accident when he had a blow on the head, losing some teeth but without loss of consciousness. Since leaving grammar school, aged 17, he had held many jobs for short periods.

He gave a 4-year history of drug-taking, but denied taking amphetamines. He smoked cannabis regularly four times a week, L.S.D. had been taken on about thirty occasions, and mescaline and 'Mandrax' (diphenhydramine and methaqualone) occasionally.

On examination he was unkempt, withdrawn, and uncommunicative. He was emotionally flattened, and at times his thoughts were disjointed. There were no abnormal physical signs.

At air encephalography the diameters A, B, and C of the left lateral ventricle were all slightly increased (fig. 7). The width of the third ventricle was within normal limits. The left trigonal region was rather "square". The area measurement E was increased on the left side.

E.E.G. was normal.

*Case 5*

A 20-year-old clerk complained of loss of concentration and memory loss for recent events over the previous 10 months. He had become irritable and depressed and volunteered to being increasingly inefficient and careless at work. His birth had been normal, and there was no history of significant illness or trauma.

He had started taking amphetamines at school when 14 years old, and within a year was smoking cannabis. This had become the main drug of dependence, although he had taken others, including two doses of L.S.D. Cannabis had been smoked once or twice daily over the past 18 months.

On examination he was mentally retarded, thinking with obvious difficulty, and with poor memory for recent events. There were no other abnormal neurological signs.

At air encephalography the diameters A and B were within normal range, but the diameters C were slightly increased. The width of the third ventricle was at the upper limit of normal. The area measurement E was within normal limits.

*Case 6*

A 22-year-old unemployed man complained of difficulty in recalling recent events, and also of periods of amnesia with occasional headaches. He described permanent alteration of vision after some years of drug abuse, with alteration of bright lights into colors: "On a sunny day I have a lot of extra color without drugs—that's very nice". There was no history of birth injury, trauma to the head, or significant past illness.

He had a 7-year history of drug abuse, starting with cannabis and amphetamine at age 15. Cannabis remained the chief drug, although he had also taken a large amount of L.S.D. and occasional barbiturates. He left school aged 15 and then had 4 months at sea with the Merchant Navy. Since then he had been unable to hold any job for long, and has not worked for the past 4 years. Over the previous 18 months his mental state had rapidly deteriorated, with intermittent confusional states and paranoid psychosis. There seemed to be a striking difference between the bright lively youngster of 14 who was interested in fishing and shooting and was able to strip down and maintain a motorcycle, and the retarded, slothful, emotionally labile, and intolerant man of 22.

He had no abnormal neurological signs.

At air encephalography the diameters A and B were within the normal range but the C diameters were increased (fig. 8). The width of the third ventricle was towards the upper limit of normal, and the right temporal horn was larger than the left. The area measurement E was increased on both sides.

*Case 7*

A 26-year-old unemployed clerk complained of poor memory and frontal headache. He described several brief episodes over recent months during which he noticed a sensation of heat in the head, pounding in the temples, and loss of vision followed by visual hallucinations. There was no history of birth injury or any subsequent trauma to the head. He had had eczema at age 2 and had been treated with sedatives off and on for several years.

He first smoked cannabis at age 15, but stopped while in the Army for 4 years. He described regular and heavy dependence on cannabis over the past 2 years. A large amount of L.S.D. had been taken but not much barbiturate or amphetamine.

Abnormal traits were characterized by superficial personal relationships, failure to develop any continuing interest, and inability to learn from experience or to apprehend any long-term consequence of his behavior. There were no abnormal neurological signs.

At air encephalography the diameters A and B were within the range of normal, but the C diameters were slightly increased. The width of the third ventricle was towards the upper limit of normal. The surface sulci frontally were rather prominent. The area measurement E was towards the upper limit of normal.

E.E.G. showed paroxysmal slow activity in all areas with no focal abnormalities, and the background pattern was normal.

*Case 8*

A 28-year-old man had been severely psychiatrically disabled with a schizophrenic illness marked by episodes of excitement and confusion for over 5 years. There was no history of birth injury or other significant past illness.

At age 16 he started taking amphetamines, having left his work as a clerk and joined a group of potato pickers. At this time he also started drinking alcohol heavily. When 17 he smoked cannabis for the first time, and had continued taking it as the preferred drug since then. With money received as compensation for a facial injury he financed a visit with friends to a Spanish island, where he drank a lot of wine, smoked cannabis heavily, and took five doses of L.S.D. despite the fact that it produced devastating reactions. He remained there for 6 months and was probably in a very confused and hallucinated state most of that time, 6 months later he was admitted to Whitchurch Hospital with a schizophreniform reaction, and he has been under continual treatment since then.

At recent examination there were no abnormal neurological signs, but over the previous 6 years there have been frequent episodes of apparently spontaneous wide dilatation of the pupils.

At air encephalography the diameters A and B were within the normal range but the C diameters were increased. The width of the third ventricle was outside normal limits, particularly posteriorly. The left temporal horn was dilated and the surface sulci over the left hemisphere were prominent. The area measurement E was increased on both sides.

E.E.G. was normal.

*Case 9*

This 21-year-old man complained of poor concentration and memory over the past year. He had no significant past illness, head injury, or birth trauma.

He started taking amphetamines when 14 years old and was soon smoking cannabis and taking barbiturates. From the age of 17 he had occasional L.S.D.

and intravenous morphine, but cannabis and barbiturates had remained the main drugs. The recent clinical picture was that of an excited overactive state with periods of confusion. He seemed to have a blurred and telescoped view of his drug-taking history.

On neurological examination he was found to have some clumsiness of fine movement of the left hand.

Serum-aspartate-aminotransferase was raised to 37 I.U. There was no history of jaundice or excessive alcohol intake, and no evidence of hepatomegaly.

At air encephalography the diameters A, B, and C were well within normal limits. The width of the third ventricle was also within normal range. The left temporal horn, however, was much dilated. The area measurement E was well within normal limits.

*Case 10*

This 26-year-old man was admitted as an emergency with an overdose of L.S.D. He had been unemployed for several years after only a year at university, where he had become less able to continue his work after starting taking drugs. There was no history of birth injury, significant past illness, or trauma.

He gave a 7-year history of drug addiction, starting with amphetamines and cannabis at age 19. By the time of admission he was taking large amounts of these drugs as well as occasional L.S.D. He admitted to being in a perpetual state of confusion and carelessness and complained of poor memory.

On examination after recovery from the acute episode of L.S.D. intoxication, it was noted that he had persistent clumsiness of fine movement of the left hand, but no other neurological signs.

At air encephalography the diameters A and B were within the normal range but the diameters C were increased. The width of the third ventricle was towards the upper limit of normal. The right temporal horn was a little dilated. The area measurement E on the right side was towards the upper limit of normal.

An E.E.G. showed abnormal slow activity in the temporal lobes on both sides.

## RESULTS

Descriptions of individual air encephalograms have been given with the case histories. Comparison of the diameters of the lateral and third ventricles showed that, between the control and the drug-abuse groups, the diameters A and B were not statistically different. But the diameters C and D and the area measurement E showed more striking changes, and these were statistically significant. The table shows the measurements and distribution of C, D, and E for the controls and the drug-abuse group. We could not measure D in one control where the posterior diameter of the third ventricle was not well enough shown. The areas E measured by planimetry are shown in fig. 3.

Besides these differences in the bodies and frontal horns of the lateral ventricles there were other isolated abnormal features in the drug addicts. Temporal-horn dilatation was found in five of the cases, and in one of those the dilatation of the horn was the sole abnormality found (case 9). The trigonal region of the lateral ventricles as seen in the prone films was also considered abnormally "square" in three of the cases (see fig. 4), and surface air showed dilated sulci (>3 mim.) in two of the cases in the frontal region. There were none of these abnormalities in the control group.

Study of the diameters A, B, and C and area E showed that on average the left lateral ventricle is slightly larger than the right in both the control and the drug-abuse groups, but that this difference is magnified in the drug-abusers. This asymmetry is not uncommon, but has never been satisfactorily explained. Its relationship to left-sided cerebral dominance is of interest, and in this respect it should be noted that all our patients were right-handed.

MEASUREMENTS C AND D AND AREA MEASUREMENT E FOR THE CONTROL AND DRUG-ABUSE GROUPS

| | C (mm.) | | D (mm.) | | E(cm.²) | |
|---|---|---|---|---|---|---|
| | R | L | A | P | R | |
| Controls: | | | | | | |
| A | 3 | 4 | 3 | 3 | 1.8 | 2.4 |
| B | 4 | 4 | 3 | 4 | 2.6 | 3.7 |
| C | 3 | 3 | 4 | 5 | 1.6 | 1.2 |
| D | 4 | 4 | 4 | 4 | 1.8 | 1.8 |
| E | 5 | 5 | 4 | ? | 1.4 | 1.6 |
| F | 7 | 8 | 4 | 6 | 3.4 | 3.0 |
| G | 6 | 6 | 5 | 6 | 3.2 | 3.1 |
| H | 7 | 7 | 5 | 7 | 3.0 | 3.1 |
| I | 5 | 5 | 7 | 6 | 2.4 | 2.8 |
| J | 5 | 5 | 4 | 4 | 3.3 | 3.1 |
| K | 4 | 4 | 3 | 3 | 2.9 | 2.6 |
| L | 4 | 5 | 4 | 5 | 2.9 | 3.2 |
| M | 5 | 5 | 3 | 3 | 1.6 | 1.8 |
| Cases: | | | | | | |
| 1 | 7 | 8 | 5 | 6 | 4.6 | 5.8 |
| 2 | 9 | 9 | 5 | 8 | 4.0 | 4.4 |
| 3 | 4 | 9 | 8 | 8 | 2.6 | 4.9 |
| 4 | 5 | 10 | 4 | 5 | 2.9 | 4.1 |
| 5 | 6 | 6 | 7 | 6 | 3.2 | 3.0 |
| 6 | 9 | 9 | 6 | 6 | 4.0 | 4.3 |
| 7 | 6 | 6 | 7 | 7 | 3.2 | 3.4 |
| 8 | 8 | 8 | 8 | 10 | 4.3 | 4.6 |
| 9 | 5 | 5 | 4 | 5 | 2.1 | 2.2 |
| 10 | 6 | 6 | 6 | 6 | 3.4 | 2.4 |
| Mean of controls | 4.8 | 5.0 | 4.1 | 4.7 | 2.5 | 2.9 |
| Mean of cases | 6.5 | 7.6 | 6.0 | 6.7 | 3.4 | 3.1 |
| P | <0.05 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |

Key to symbols: R = Right. L=Left. A=Anterior. P=Posterior. Analysis using student's *t* test.

## DISCUSSION

Significant cerebral atrophy is rare in young people. It may happen after head injury but can be attributed to this only when there has been post-traumatic amnesia of several hours or evidence of focal neurological damage at the time of the injury.[4] None of our patients who had had minor head injuries (cases 1, 3, and 4) would satisfy these criteria, and we do not consider that their head injuries played a part in the enlargement of the ventricular system. Other causes for cerebral atrophy include head injury at birth, especially in prolonged labor or in conditions causing anoxia; and some cases may also be due to hypoplasia rather than atrophy, and differentiation may not be possible. Severe infections in childhood when encephalitis has supervened, congenital syphilis, and toxoplasmosis may cause atrophy, as may congenital or acquired vascular lesions. Other causes include hereditary disease such as Huntington's chorea. Diffuse demyelinating conditions can produce quite rapid cerebral atrophy in the second and third decade. It must be stressed that cerebral atrophy indicates irreversible brain damage. We found no such causes for cerebral atrophy in this series of ten drug addicts.

Booker et al [3] emphasized that generalized abnormal ventricular size is usually found in diffuse neurological disease rather than focal neurological conditions. They showed that epilepsy is not associated with dilatation of the cerebral ventricles unless the fits are extremely severe and extend over a long period of time. In their series, which is very relevant to our work, there were twenty-five non-neurological cases of a mean age of 32.2 (which is well above our controls and drug-abuse series), and in this group they found a mean lateral ventricular area measurement, determined by planimetry, of 2.90 sq.cm. for the right ventricle and 2.98 sq.cm. for the left. These figures agree with our normal control group and emphasize the difference from the addicted group.

In this epileptic series of thirty-six patients it is interesting that the mean lateral ventricular area was less—2.54 sq.cm. on the right and 2.60 sq.cm. on the left—both in the normal range. Only in the cases of frank neurological disease did the measurements approach those of our drug-abuse series—i.e., right side 3.9 sq.cm. and left side 4.63 sq.cm.—for this age group. We would emphasize, therefore, that the finding of this ventricular size in our drug-dependent group at this age is abnormal, and although these figures might be found in the seventh or eighth decade they are abnormal for this age-group.

The films demonstrate a definite pattern of cerebral atrophy. Apart from the

generalized dilatation of the body and posterior part of the frontal horns of the lateral ventricles, the most striking feature is, perhaps, the dilatation of the lateral and to some extent the inferior angle of the ventricle, and the falling away of the floor, combined with the dilatation of the third ventricle. Although no specific conclusions can be drawn from these changes—because similar changes may be seen in parkinsonism and in the atrophy of old age and arteriosclerosis, for example—the appearances do nevertheless suggest that the worst damage is in the region of the caudate nuclei, basal ganglia, and the structures adjacent to the third ventricle. The occurrence of an isolated temporal horn dilatation in one case is of interest, but in another four cases this appearance was combined with the generalized changes in the bodies and frontal horns.

The brains of monkeys given isotope-labelled cannabinols intravenously showed concentration of the drug in the frontal lobes and cortex, geniculate bodies, cerebellum, caudate nuclei, and putamen [5]—all structures near the third and lateral ventricles. After 24 hours the drug had spread uniformly throughout the brain. The fat solubility of the cannabinols [6] make it likely that they would accumulate in nervous tissue, with its high fat content.

There is a very interesting parallel between the picture shown by encephalitis lethargica and that of chronic abuse of cannabis and L.S.D. This was evidenced in some of our cases by a reversal of sleep rhythms, hallucinations and mental changes. Hall, writing about the epidemic of encephalitis lethargica, [7] commented:

"If the public asylums have seen little of the disease, the homes of sufferers and the police courts for juvenile offenders told a different story, while in adults the history of 'not being the man he was', inability to work, being irritable and difficult, a loss of memory and a falling-off in moral character are signs of this infection".

Again, Hall mentions the extreme apathy produced by this disease, which is followed by catatonia, and this indeed is another effect of cannabis both in animals and man.

In encephalitis lethargica, the worst damage was in the basal ganglia, midbrain, thalamus, and floor of the third ventricle, and this is the very area where we have demonstrated atrophy in our patients. Kennedy [8] postulated that, in encephalitis lethargica, many of the symptoms were due to interference with afferent impulses, and the same has been suggested about the action of cannabis and L.S.D.

Our findings emphasize the importance of considering organic nervous symptoms and signs in any long-term assessment of the use of cannabis such as is contemplated in India. The area of the brain showing damage in our cases suggests it would be interesting to examine the cannabis-smoking habits of cases of Parkinson's disease in the Indian population—Parkinson's disease being relatively common in India.

Work on the impairment of recent memory in monkeys given cannabis is also pertinent. [9] Several of our patients complained of poor memory for recent events.

von Zerssen et al.[10] studied the diameter of the third ventricle in drug abusers and controls by echoencephalography, finding that this measurement was 7 mm. or more in the addicted group and less than 7 mm. in the controls. Details of the drugs used and the age-groups were not mentioned.

Cerebral atrophy is known to occur in alcoholism. [11] Kálám an found dilatation of the third ventricle in almost all of eighty-seven patients regularly drinking alcohol.[12] Only two of our cases (nos. 8 and 10) had taken much alcohol, and alcoholism is unusual in heavy cannabis smokers. The pattern of drug taking was similar, in that most of our patients started on amphetamines and within a short time were smoking cannabis regularly. L.S.D. had also been taken, but cannabis became the predominant drug in all cases. For instance, if cannabis had been smoked regularly three times a week for 3 years, it would have been taken over 450 times, and this should be compared with the usual L.S.D. average of ten to twenty doses. It is important to stress that morphine, heroin, or cocaine had not been taken in any significant quantities. Some patients had temporarily ceased to take drugs while in detention or in the Army, and it was therefore impossible to relate the length of history to total dose or to the extent of cerebral atrophy.

It may be suggested that our cases were abnormal before they began smoking cannabis, but in at least three cases where we know the history intimately these individuals were entirely normal before they started drug-taking. It would be

surprising to find cerebral atrophy of no apparent cause in consecutive cases, selected only by their histories of chronic cannabis dependence.

Our findings indicate that there is a particular pattern of cerebral atrophy in a series of young men who smoked cannabis. Although amphetamines and L.S.D. may have an added effect, they are rapidly metabolized and excreted and would not seem likely to have the cumulative effect on nervous tissue of the fat-soluble components of cannabis. We feel that our results suggest that regular use of cannabis produces cerebral atrophy in young adults.

For many years the production of cerebral atrophy in professional boxers was not realized. We would suggest that a similar state of affairs is happening in relation to drug abuse. Far too much attention has been paid to psychological and behavioral disturbances, without relating these to the possibility of permanent damage to the brain.

This work on man indicates an urgent need for further studies of the neurological consequences of drug abuse, and particularly the long-term effects of cannabis smoking. Further radiological and neuropathological studies on man and other primates are suggested. Serial psychometric and encephalographic studies in the young drug-taking population would seem worth while.

We thank Prof. W. D. M. Paton, University of Oxford, and Prof. K. T. Evans, of Cardiff Royal Infirmary, for helpful criticism; Miss E. H. L. Duncan, lecturer in statistics, University of Bristol; Mr. J. Banham for the photographic work; and Mrs. Linda Nash for the secretarial help.

Requests for reprints should be addressed to A. M. G. C. and J. L. G. T.

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## Cannabis and Alcohol: Effects on Simulated Car Driving and Psychological Tests

(By Ole J. Rafaelsen, Professor of Biological Psychiatry, Psychochemistry Institute, Rigshospitalet 9, Blegdamsvej, DK-2100, Copenhagen, Denmark)

Paper read at: The Pharmacology and Experimental Psychology of Cannabis and its Derivatives. A Symposium arranged by The Institute for the Study of Drug Dependence at The Ciba Foundation. May 16th and 17th, 1972.

*Editorial summary*

1. The tests described by Professor Rafaelsen were conducted under strict controls. Placebos (harmless substances with undistinguishable tastes) were alternated in a random manner with cannabis and alcohol. Both the cannabis and placebo were baked into identical small brown cakes, with the THC dosage in the cannabis cakes standardized at 200, 300, and 400 mgs. of 4% THC. A car simulator was used to measure braking time, starting time (in response to green lights), and the subjects' ability to estimate time, distance, and speed. In

addition, various psychological tests were administered, including memory and concentration tests.

2. Many similarities between the effects of cannabis and alcohol on driving were found, but there were also important differences quantitatively and qualitatively. The subjects ability to estimate time and distance was, in general, much more strongly affected by cannabis than by alcohol. In the estimate of Professor Rafaelsen, "Cannabis has such pronounced effects on skills and judgment essential for driving to make motoring during cannabis intoxication a hazardous undertaking."

3. In psychological tests with small labyrinths of graduated complexity, cannabis resulted in more errors and slower performance than alcohol. Alcohol resulted in reduced performance only on the most complicated of the four labyrinths; cannabis affected performance on three of the four labyrinths.

4. In another test designed to measure short-term memory, the subjects were required to perform serial subtractions of seven. Alcohol caused a 46% increase in time score; cannabis, at the intermediate dosage of 300 mgs., a 57% increase. There were also more errors with cannabis than with alcohol.

This study was prompted by our demonstration of cannabis metabolites in human urine after oral administration of cannabis to volunteers. Our hope was to be able to compare psychological observations with pharmacokinetic studies in a field, which has been marred by the absence of exact methods.

We are still unable to say whether we will succeed in a correlation of psychological and chemical findings, and I shall today limit myself to talk on the psychological data. My presentation will fall in two parts stemming from the same series of experiments: simulated driving and a battery of psychological tests.

We chose the oral route of cannabis administration as our previous demonstration of cannabis metabolites in urine had shown more consistent findings after oral intake than after smoking, and we supposed dosage to be more constant intra- and inter-individually by this route. The research design included principles of placebo, double-blindness, dose-response, tests for reproducibility and training effects, the volunteers acting as their own controls. The effect of a standard dose of alcohol was included in the program for the sake of comparison.

*General research plan*

The subjects were 8 male volunteers between the ages of 21 and 29, in good physical and psychic health. MMPI (Minnesota Multi-phasic Personality Inventory) showed normal profiles, and they had no excessive use of cannabis or alcohol. 3 had never tried cannabis, 5 for 1 to 15 times, no one more than once a week.

The study lasted three months. After a training period each subject was tested on nine experiment days with weekly intervals. Each experiment day included three sessions: *1.* before drug administration ('pre-test'); *2.* under drug influence ('drug-test'); *3.* the following morning ('post-test').

Cannabis was baked into small brown cakes in amounts of 200, 300, or 400 mg of a resin contained 4% Δ 1-tetrahydrocannabinol (THC). For placebo cakes cannabis with a minimal content of THC was used.

Alcohol was given in fruit juice in a dose of 70 g, leading to blood alcohol concentrations around 100 mg/100 ml one hour later.

The combined administration of alcohol and cannabis was not undertaken, but the subjects were unaware of this precaution. The use of placebo technique is not synonymous with achievement of blindness, and it is doubtful whether this can be obtained with alcohol; on the other hand, we have indications that it was probably obtained with cannabis. None of the subjects could differentiate by taste between cakes containing active and inactive cannabis, and they had difficulties assessing the various doses.

The whole experimental period fell into three parts:

In *Part I* all subjects were tested on three days with one pure placebo day, one day with cannabis 300 mg, and one day with alcohol administration.

*Part II* was an exact repetition of Part I, except that randomization led to a different order of treatment days for the individual subjects.

Finally in *Part III* the interest was on dose-response for cannabis, the subjects obtaining the three different doses of 200, 300, and 400 mg (~8, 12 and 16 mg THC) in randomized order. Placebo drink was here given on all days.

As the subjects were their own controls, results obtained before drug administration ('pre-test') were compared with results obtained while the subjects were under the influence of drug ('drug-test'), and with results obtained the following morning ('post-test'). For the comparisons were used non-parametric statistics. In general, the differences between pre-test values and post-test values were minimal and without statistical significance. Also, no statistically significant changes were found on placebo days. Most of the presentation will therefore be concerned with a comparison of pre-test and drug test results.

The 300 mg of cannabis resin used was in a pilot study judged by experienced volunteers as an average cannabis dose, and it was therefore chosen for comparison with the alcohol dose used throughout Part I and Part II of the research program.

*Simulated car driving*

The car-simulator was a Redifon Auto-Tutor. This test model is built up like the front half of a car, and a picture from a movable cyclorama is continuously projected on the windshield giving the subject the impression of driving on a variable test course. Light signals appear at arbitrary intervals. Extra equipment made it possible to record a number of functions electronically, among these brake time, start time, number of gear changes, time, distance, and speed.

Brake time: Time from red light to the subject activates the brake pedal.

Start time: Time from green light to the subject activates the accelerator.

Subjects' estimate of time, distance, and speed: The subjects were trained to estimate time, distance, and speed in two different ways: a) 'objectively' or 'intellectually' (using cognitive and outer clues): 'how long and how far do you really *think* you have been driving?' and b) 'subjectively' or 'emotionally': 'how long and how far do you really *feel* you have been driving?'.

Both cannabis and alcohol influenced average brake time and start time in the car simulator.

A dose-response type of effect was seen on cannabis, and the effect of alcohol was more pronounced than 300 mg cannabis resin and less than 400 mg cannabis resin. The effect of both cannabis and alcohol had disappeared at the post-test the following morning.

The effect of both cannabis and alcohol was somewhat less marked on start time, and here only the increase after the highest cannabis dose obtained statistical significance. However, the pattern and relative effect of cannabis and of alcohol was similar to the brake time findings. In Part III the group on 300 mg cannabis resin only contains 7 and not the usual 8 subjects, the reason being that on this occasion one of the subjects drove through 8 of the 10 red lights without activating the brake pedal, let alone making a full stop!

The subjects' estimations of time and distance showed a much stronger effect of cannabis than of alcohol. It is noteworthy that the effect of cannabis was much more marked on the 'subjective' than on the 'objective' estimations, and on the 'subjective' estimations increase above 100% and even up to 300% were seen.

How do our results compare to findings reported in the literature? As for alcohol, the effect is well-documented practically and under laboratory situations. The only study in the literature on cannabis and simulated car driving is by Crancer and his co-workers. But others are on the way from Germany and Switzerland. The results obtained by Crancer were at variance with ours, as he only found an increase in speedometer error, but not on accelerator, brake, signal, steering, and total errors. The methodologies used by Crancer et al. (1969) were, however, also different from ours. Cannabis was smoked, with the inherent difficulties in assessing actual THC uptake by the subjects. The content in the cigarettes was stated as 22 mg THC, but there are indications that the true content of the batch used was less than supposed, reducing actual dose to 8 or even 3 mg (Caldwel et al., 1969, Manno et al., 1971). Especially with a low THC-dose, it is quite probable that the psychic effects have been waning or gone when the first simulator test was taken some 30 to 60 minutes later. In addition, the car-simulator used by Crancer was basically different. In our model

the subject decides the speed and to a certain extent the route, whereas in Crancer's model the landscape simulation is obtained by a movie so that the subject is given a much more passive role. Braking or not braking was studied by Crancer, but not brake time; and brake time was as mentioned most strongly influenced among the functions recorded in our study. It has been found by Carpenter (1962) that brake time is especially valuable, when one wants to extrapolate from laboratory experiments to driving conduct under ordinary conditions in normal traffic. The generally negative results by Crancer and his group seems thus to be explainable by an analysis of different aspects of the experimental design. Our findings that the effect of cannabis was much more marked on the 'subjective' than on the 'objective' estimations of time and distance might explain the conflicting results of previous investigations in this field. I will now turn to results from a number of the psychological tests, which we applied.

*Psychological tests*

The psychological tests preceded each driving period in the car-simulator and thus were administered three times on each experiment day. The psychological test battery included:

A. *Memory and concentration tests.*—Digit span; reproduction of sentences; addition and subtraction tests; finger labyrinths; Bourdon's letter test; and a test of sentence construction.

B. *Consciousness and mood scales.*—Subjective rating (Smith and Beecher's 12 item mood questionaire), and objective rating (similar items rated by psychologist).

These tests all fulfilled the following criteria:

They should be replicable in 27 parallel versions according to the research design; they should only place a limited demand on the subjects in order to secure proper motivation; they should all have little or a controllable practice effect.

(C).—In addition, personality tests were administered on some occasions. The Minnesota Multiphasic Personality Inventory (MMPI) was used during the primary selection of subjects. Only subjects falling within the range of normality were admitted to the study. The test was repeated four months later (after the completion of the experiments), and again one year later in order to ascertain any possible long-term changes in personality.

Rorschach and Association Tests were given once midway during the experimental period—before the drug administration of that particular day.

I will describe a couple of the cognitive tests, and then go on to the subjective and objective questionnaire.

*Finger labyrinths.*—These were constructed of cardboard plates and thin wooden sticks. Different degrees of complexities were obtained by changing the instructions from 'turn left, turn right' to 'turn twice to the right, turn one time to the left' and furthermore by the introduction of blind alleys. The test is supposed to measure aspects of short-term memory. Errors and time were scored. Errors for forgetting the instruction, and time in seconds for passage through the labyrinth. The results show that both errors and time scores for the passage were generally more influenced by drug, the more complex the labyrinths and instructions. In all four labyrinths, except the most simple, both cannabis and alcohol increased time spent by some 20%, and these changes obtained statistical significance for cannabis, but not for alcohol. Regarding *errors*, the effect of cannabis was more marked than the effect of alcohol, cannabis affecting the three more complicated labyrinths, alcohol only showing a clear effect on the most complicated of the four labyrinths.

*Serial subtraction of sevens.*—This test is supposed to measure aspects of short-term memory as well as fully-established skills. Time and errors were scored. Alcohol caused a 46% increase in time score, cannabis 300 mg. a 57% increase, the latter result being statistically significant; a tendency to more errors was seen on cannabis, but not on alcohol.

With regard to dose-response to cannabis in the cognitive tests, this was demonstrated for time in both finger labyrinths and serial subtraction of sevens. whereas for errors the picture was less clear. Errors in the most complicated of the four finger labyrinths showed a dose-response pattern, whereas this was absent in the serial subtraction of sevens.

*Smith and Beecher's mood questionaire.*—This was originally designed to measure 'mental clouding' and other subjective effects of morphine. It consists of 12 questionnaire items to be rated on a seven-points scale. The items fall into categories of 'mental clouding', 'inactivity', 'anxiety', 'unfriendliness', 'shyness', and

'sadness'. For our purpose we added two more items: 'motivation' and 'feeling of intoxication'. The objective questionaire was rated by the psychologist and consisted of 11 items covering similar modalities.

Results of the mood questionaire showed that the items 'slow-mindedness', 'dreaminess', and 'grogginess' appeared to be closely related to the intake both of alcohol and of cannabis, and the effects were statistically significant; on 'inactivity' an effect of cannabis was found, alcohol influencing this item somewhat less. Dose-response pattern for cannabis was not seen for the first three of the above-mentioned categories, but it was seen for 'inactivity'.

The objective rating by the psychologist parallel to the mood questionaire showed effects of both cannabis and alcohol on 'grogginess'; of cannabis, but not of alcohol on 'sleepiness'; of alcohol, but not of cannabis on 'talkativeness and elation'.

Comparing the results of the mood questionaire and of the objective rating showed a very marked agreement between subjects and experimenters as to quality of intoxication. 8 out of 8 subjects rated themselves intoxicated by alcohol after alcohol administration, and the objective ratings were in complete agreement with this. Whereas wrong classifications after placebo was seen for one subject after alcohol, three subjects rated themselves intoxicated by cannabis after placebo administration. An experimenter rated one subject intoxicated by cannabis after placebo. As to degree of cannabis intoxication both mood questionnaire (subjective rating) and the objective rating by psychologist showed a clear and virtually identical dose-response pattern.

In a general view of the psychological tests, the effect of cannabis and of alcohol on *cognitive* functions were qualitatively alike although quantitative differences were found on some tests. Comparing 70 g of alcohol and 300 mg of the cannabis resin used, more results obtained statistical significance after cannabis than after alcohol administration. The impairment on cannabis was only moderate in tests of sustained attention and attention span where the task is fairly simple requiring repetitive reactions of a uniform kind, but no alternating reactions or operations. In the task where every step depends on the previous one, the effect of cannabis was most clearly seen. This is in accordance with the findings of Melges et al. (1970) using a Goal Directed Serial Alternation Test. This phenomenon may explain the discrepancy in the effect of cannabis on time score versus the effect on errors. Time scores were increased by cannabis in a great number of the tests used, but only on the longest and most complicated tasks did the error score obtain statistical significance, and it is noteworthy that the dose-response patterns on time scores were among the most consistent results.

Consciousness and mood ratings by subjects and experimenters showed many similarities between cannabis and alcohol effects, but distinction was obtained on some items, in accordance with the finding that the subjects in most cases were able to decide the quality of intoxication.

In conclusion, we have found effects of cannabis (and of alcohol) on simulated car driving and on a psychological test battery. The effects of cannabis was found both in behavioral tests and in phenomenological ratings; both in simulated car driving and in the psychological test battery. Many similarities between the effect of cannabis and alcohol were found, but also a remarkable amount of differences, qualitatively and quantitatively.

*Summary*

It seems justified to draw the following three conclusions:

1. Cannabis and alcohol produce two different kinds of intoxication.
2. Dose-response effects of cannabis is seen on behavioral and phenomenological aspects.
3. Cannabis has such pronounced effects on skills and judgments essential for driving to make motoring during cannabis intoxication a hazardous undertaking.

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[From Nature, Oct. 10, 1970]

## Preliminary Experiments on the Chemistry and Pharmacology of Cannabis

(By E. W. Gill, W. D. M. Paton, R. G. Pertwee, Department of Pharmacology, University of Oxford)

*Editorial summary*

1. There are at least six pharmacologically active components in cannabis. Their effects on mice include a lowering of the body temperature, catalepsy, analgesia, and an extension of barbiturate sleeping time—with doses of 25 to 200 milligrams per kilogram of body weight.

2. Cannabis, in experiments conducted by different scientists, has resulted in lower body temperatures in rats. The drop in temperature varies with the dose and with the method of administration. A drop of as much as 8 degrees Centigrade (15 degrees Fahrenheit) was produced with a dose of 25 mgs. per kg. of body weight.

3. The cataleptic effect of cannabis on mice is measured by the proportion of time they spend motionless when straddling a wire ring.] Catalepsy is a condition in which consciousness and feeling are suddenly and temporarily lost and the muscles become rigid.] Crude cannabis elicits detectable cataleptic effects at 200 mg. per kg. of body weight when administered intraperitoneally, or 100 per kg. of body weight when administered subcutaneously. If repeated daily subcutaneous doses are given, the level of catalepsy achieved increases up to 8 days, indicating a cumulative response.

4. A preliminary study was made of the lethality of cannabis injected each day intraperitoneally at various dose levels. A single dose of 5,000 mg. per kg. of body weight killed all of 5 mice; 1,000 mg/kg killed all of four mice in four days; 500 mg/kg killed 2 of 5 mice in 45 days; 100 mg/kg caused no deaths in 50 days. These results suggest either a cumulative effect of the drug or a summation of its effects.

5. Cannabis contains, apart from THC, at least 5 other pharmacologically active components. In the water soluble fraction, atropinic activity has been found. [Atropine is a poisonous alkaloid derived from belladonna and similar plants, which is used to relieve muscle spasms and dilate the

pupil of the eye.] It may be this substance that is responsible for the effects of cannabis on salivary secretion and on the heart rate.

There are at least six pharmacologically effective components of cannabis. Their effects on mice include a lowering body temperature, catalepsy, analgesia and an extension of barbiturate sleeping time, with doses from 25 to 200 mg/kg.

In this investigation we have used tincture of cannabis BPC. This is a commercial product prepared by extracting the leaves and flowers of *Cannabis sativa* with cold alcohol, evaporating the solvent and dissolving the resinous residue in fresh ethanol. The plant material is grown in Pakistan and imported into Britain under license. The crude extract, a complex mixture (1), was fractioned according to the procedures developed by Korte and Sieper (2). Solvent was removed *in vacuo* and the resin was extracted with petroleum spirit. This fraction, solution in petrol, was freed from chlorophylls and carotens by chromatography on alumina and the fraction containing phenol was purified further by counter-current distribution. Three principal functions were obtained: (1) $\triangle_1$-tetrahydrocannabinol ($\triangle_1$-THC) Fig. 1*a*; R=*n*-$C_5H_{11}$), frequently identified as the major physiologically active component, constituting 2.4 per cent of the tincture base, (2) A second single component, very similar to $\triangle_1$-TCH, which was subsequently identified as the hitherto undescribed *n*-propyl analogue of $\triangle_1$-TCH) Fig. 1*a*, R=*n*-$C_3H_7$). The structure of this compound was deduced from its infrared, ultraviolet, NMR, and mass spectrum and has been confirmed by synthesis. The compound represented 2.0 per cent of the crude tincture base and is therefore a quantitatively significant component of the crude extract. (3) The third fraction, least mobile in the counter-current system used, was a complex mixture, characterized by strong absorption at 1,600–1,800 $sim^{-1}$ (suggesting that it contained partially oxidized components), and has not been further fractionated.

The residue that was unsoluble in petrol were extracted by shaking with water, and the aqueous extract was analyzed by high-voltage paper electrophoresis. A strip of the paper was subjected to color reactions, and the remainder divided into six parts and eluted.

*An atropinic substance*

We readily detected a spot with the mobility and color reactions of trigonelline, a previously identified constituent of cannabus. Trigonelline was found to have little pharmacological activity, being about $10^5$ times less active as an agonist than acetyleholine, and with no detectable antagonist activity. But in the eluate from this region of the strip, an acetyleholine-antagonizing material was found, with a slow course of action comparable with that of atropine, ineffective against histamine and such that the material from 1 ml. of tincture produced a fourteenfold dose-ratio in a 5 ml. organ bath. This is equivalent to about 1 $\mu$g/g of resinous residue; but the stropine-like component is liable to acids and alkalis, and the losses, although known to occur, have not been estimated.

A second, more rapidly moving spot was also found, with an electrophoretic mobility comparable with that of the methyl or ethyl estera of trigonelline (but not that of choline). These esters are both gut stimulants; the methyl ester is like acetyleholine, but 1/200 times as potent; the ethyl ester is roughly 1/2,000 times as potent as acetyleholine, but has a flatter log-dose-response curve. Both are sensitive to lachesine but not (on the intestine) to hexamethonium. The eluate from the front of the fast spot resembled the metyl ester pharmacologically; that from the rear part had a log-dose-response curve flattened in the same way as that of the ethyl ester.

There is therefore evidence of the presence of an atropinic and two muscarinic substances in the watery extract as well as of the relatively inert trigonelline. None of these, however, has yet been obtained in sufficient quantity for chemical identification. If the ethyl ester is in fact present, it may well be an artefact resulting from esterification of trigonelline by solvent ethanol. The acetylcholine-like components could contribute to the irritant effect of the smoke. THC in a dose of 3 mg/kg was found, in the cat under chloralose, to affect neither chorda-simulated salivary secretion nor the bradycardia in response to vagal stimulation, and it is therefore probable that the atropine-like material, rather than THC, chiefly causes the salivary and heart rate effects of taking cannabis. But because THC can reduce acetylcholine output from the parasympathetic nerve plexus of the intestine (see below), this depression of transmitter release may potentiate the atropinic action.

The chief active principles of cannabis have long been known to be insoluble in water and strongly lipophilic. The octanol: water partition ratio of THC was too high to be measured, but exceeded 500:1 (comparable with trichloroethylene and higher than most barbiturates). A saturated solution of THC in saline contains about 5 μg/ml. To obtain crude cannabis, THC or propyl-THC in saline solution, they were mixed with 0.5 to 2 times their weight of 'Tween 80.' Both cannabis and the pure substances act as anti-frothing agents, but none will reduce the surface-tension-lowering activity of the Tween solutions. Because we still do not know which of the pharmacologically active fractions are absorbed when cannabis is smoked or ingested, experiments were made with crude cannabis as well as with THC and propyl-THC.

*Hypothermic action*

Miras(3) reported that cannabis lowers the body temperature of rats. This response, tested at an environmental temperature of 20° C, was confirmed in mice and found to be related to the dose. Intraperitoneally, 200 mg/kg produced a peak fall of 1° C. Intravenously, 12 mg/kg was ineffective, and "5 mg/kg produced in six mice a mean peak fall of 2.5° C, with recovery over a period of 30–40 min; the effect increased with increasing dosage in both magnitude (to 8° C) and duration (over 8 h). There may be peripheral factors contributing to the hypothermia, but the principal action of cannabis seems to be central. We have confirmed the observation(4) that it is effective intracerebrally. Further, it is considerably more effective by this route than when given intravenously; a dose of 25 mg/kg injected into the cerebral ventricles produced a hypothermia lasting over 8 h, with a peak full of 6° C. It was already clear(4) that the intracerebral route was more effective than the intraperitoneal route in producing hypothermia; but this might have been the result of loss of drug during passage through the liver during absorption of the intraperitoneal dose *via* the portal vessels. The fate of any of the intracerebral injection that reaches the circulation should, however, be comparable with that of intravenously given drug. THC itself has now been shown(5) to produce hypothermia in mice when given intraperitoneally.

Because hypothermia itself both changes animal behavior and alters physiological and pharmaceutical responses, so that some of the actions attributed to cannabis could have been secondary to the body temperature change, we have felt it necessary to repeat some of the previous work in conditions where significant hypothermia will not occur. All the experiments that follow, therefore, on catalepsy, analgesia and prolongation of sleeping time, were made with the mice in an environment at 30° C, known to be their thermal neutral zone (ref. (6) and unpublished work of R. G. P.).

*Catalepsy*

The cataleptic effect of cannabis (7) in the mouse has been developed into an objective assay, based on the proportion of time spent motionless when straddling a wire ring. Assays were four to nine point with seven to nine replications, suitably randomized. Control tests were made with "Tween 80" solutions. Intraperitoneal or subcutaneous injections were used. All experiments were made at 30° C. Crude cannabis elicits detectable cataleptic effects at 200 mg/kg intraperitoneally or 100 mg/kg subcutaneously, and nearly maximal effect at about 500 mg/kg with duration greater than 4 h. THC was found to be active at 5 mg/kg; propyl-THC was found to be 4.8 times less active. The THC content could account for the bulk of the cataleptic effect, but comparison of the time course of action of crude cannabis with that of THC and propyl-THC suggests that propyl-THC contributes significantly to the earlier part of the response, THC itself acting relatively slowly.

If repeated daily subcutaneous doses of 100 mg/kg crude cannabis are made, the level of catalepsy achieved increases up to 8 days, indicating a cumulative effect. The recovery from the daily dose seemed faster at the end of the period than at the start. The results were reminiscent of the fat-soluble barbiturates, with which both cumulation and tolerance occur.

The cataleptic response was studied because it was an animal response which could be related to certain aspects of the human experience with cannabis. The dose required to produce the effect in mice, whether of pure THC or in terms of the THC content of the resinous residue (2.4 per cent), is roughly ten times the human effective dose when expressed per unit weight. If one compares, for a range of centrally active drugs, the doses per kilogram used to produce the characteristic actions of the drugs in mice or rats with the corresponding doses per kilogram of the pharmacopoeia, the mouse/man ratio ranges from about

2 to 100, and with some drugs the total dose for a rat is comparable with the total dose used in man. This arises, at least in part, from the more rapid turnover of drug in small animals, and is also influenced by the route of administration and the intensity of the effect studied. So far as the doses found necessary in the experiments in this paper are concerned, therefore, there is no reason to doubt the relevance of the observations, *mutatis mutandis*, to human experience.

*Analgesia*

To test for analgesic action, the response to intraperitoneal injection of phenylbenzoquinone (8) was used, cannabis or other drugs being given subcutaneously; all experiments were done at an environmental temperature of 30° C. Cannabis had a threshold effect at 100 mg/kg and a marked action at 200 mg/kg. Using the same technique, 0.4 mg/kg morphine and 1.2 mg/kg chlorpromazine were approximately equivalent to 140 mg/kg cannabis resin. The results are comparable with those obtained with cannabis (9) and THC (10, 11) by a variety of methods without temperature control.

We have confirmed the observation of Loewe (12) that cannabis prolongs pentobarbitone sleeping time in mice even if the experiment is made in an environmental temperature of 30° C. The effect is just detectable at 50 mg/kg intraperitoneally and increases with dose; with 200 mg/kg cannabis intraperitoneally the mean sleeping time in a group of nine mice given 50 mg/kg pentobarbitone 30 min later increased to 85 min, from a control value of 34. This prolongation was detectable 3 h after cannabis administration, but sleeping times tested 24 and 48 h after cannabis were normal, and no sign of induced enzyme activity after a single dose of cannabis was found.

It was possible that cannabis, while not itself overtly hypnotic, might potentiate barbiturate hypnosis by its own central action. A control experiment with either which is not metabolized was therefore made. With subcutaneous injection of cannabis or "Tween 80" control, and intraperitoneal injection of ether in olive oil, cannabis was found not to prolong ether sleeping time in a dose which prolonged pentobarbitone sleeping time. The evidence is therefore strengthened that cannabis interferes with microsomal degradation of barbiturates.

*Toxicity*

A preliminary study was made of the lethality of cannabis injected each day intraperitoneally at various dose levels. These experiments were made at the normal room temperature of 20° C. A single dose of 5,000 mg/kg killed all of five mice; 1,000 mg/kg killed all of four mice in 4 days; 500 mg/kg killed two of five mice; 1,000 mg/kg killed all of four mice in 4 days; 500 mg/kg killed two of five either cumulation of the drug itself, or summation of its effects. The cause of death has not yet been analyzed; but it may be noted that in cats under chloralose, THC at 2 mg/kg substantially depresses both respiration and blood pressure.

Teratogenicity in rats and hamsters (13, 14) and fetal resorptions in mice (15) have been described at dose levels of 4.2-100 mg/kg daily at the appropriate stage of pregnancy.

Muscarinic and atropinic actions by water soluble factors have been described above. The three fat-soluble fractions were tested on the guinea-pig ileum stimulated transmurally or with acetylcholine. THC, in a concentration of 1 $\mu$g/ml. upwards, was found to depress the twitch responses to transmural stimulation but not the response to acetylcholine (which was sometimes potentiated). It must therefore depress acetylcholine output by the nerve endings; in this way it resembles morphine (16), catecholamines (17) and anaesthetics (18), but it differs from them in its much slower onset of effect and very delayed recovery, still incomplete after many hours. Propyl-THC has a similar action, with some initial stimulant effect, but recovery from its effects was much more rapid, and it was less active than THC. The third (uncharacterized) fraction depressed both the twitch and the response to acetylcholine and resembled a nonspecific depressant such as occurs among higher alcohols.

The fractions were also tested on the guinea pig vas deferens stimulated by noradrenaline, by electrical stimulation with brief trains of shocks, or by stronger held stimulation with brief shocks, the latter being particularly useful in preliminary screening tests. THC and propyl-THC had no consistent effect on the response of the vas to noradrenaline. THC slightly reduced the response to field stimulation by trains of shocks. The response to strong single shocks was greatly potentiated by both THC and propyl-THC; THC was approximately three times more potent, and considerably slower in action. Thus response is insensitive to tetrodotoxin, and so presumably reflects a direct response of the

smooth muscle to the electric field. Cocaine and some other local anesthetics produce a similar potentiation.

*Accumulation in fat?*

Cannabis thus contains, apart from THC, at least five other pharmacologically active components, three water-soluble and two fat-soluble, one of which has been identified as the propyl homologue of THC. In the water-soluble fraction, atropinic activity has been found which may be responsible for the effects of cannabis on salivary secretion and heart rate in man. This effect may be potentiated by the ability of THC to depress acotylcholine output from parasympathetic nerves.

Cannabis resin given to mice lowers body temperature by up to 8° C. Because hypothermia of this degree could change the animal's responses significantly, tests for the action of cannabis in producing catalepsy, analgesia and prolongation of barbiturate sleeping time were repeated, with the mice in their thermal neutral zone, to prevent body temperature changes. In these conditions cannabis still produces analgesia and catalepsy, and still prolongs penobarbitone sleeping time. It was also shown that the sleeping time caused by a non-metabolized anesthetic (ether) was not prolonged. Doses required for these effects ranged from 25 to 200 mg/kg according to route of injection. In preliminary toxicity tests the $LD_{50}$ for a single dose lay between 1,000 and 5,000 mg/kg: for doses repeated daily it lay between 500 and 1,000 mg/kg.

Finally, in view of the report from a university survey (19) that of 153 students who had taken cannabis, 72 per cent took it daily or more often, attention should be paid to the fat-solubility of certain of the active principles of cannabis, their prolonged action, and the liability of cumulation.

This work has been supported by a grant from the Medical Research Council.
Received June 5, 1970.

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## LEAGUE OF NATIONS

### SECOND INTERNATIONAL OPIUM CONFERENCE

### MEMORANDUM ON HASHISH

(Submitted by Dr. Mohammed Abdel Salam El Guindy, First Delegate of Egypt)

*Editorial summary*

1. The memorandum which follows was presented in November 1924 to the Second International Opium Confer-

ence of the League of Nations by the Egyptian representative, Dr. El Guindy. Its inclusion is pertinent because the Egyptians have probably had more experience than any other people with the social devastation wrought by the extensive use of hashish.

According to Dr. El Guindy, hashish was recognized as the principal cause of insanity in Egypt. It is noteworthy that Egypt at the peak of its hashish epidemic was estimated to have used 140,000 pounds of hashish per year—a figure which may not be much greater than the current consumption of hashish in the United States, given the fact that seizures alone in fiscal 1972 totaled 10,000 lbs.

2. "Taken in small doses, hashish at first produces an agreeable inebriation, a sensation of well-being and a desire to smile; the mind is stimulated. A slightly stronger dose produces a feeling of oppression and discomfort. There follows a kind of hilarious and noisy delirium in persons of cheerful disposition, but the delirium takes an extreme form in persons of violent disposition.

3. "Hashish absorbed in large doses produces a furious delirium and a strong physical agitation; it predisposes to acts of violence and produces a characteristic strident laugh. This condition is followed by a veritable stupor, which cannot be called sleep. Great fatigue is felt on awakening, and the feeling of depression may last for several days. . . . The habitual use of hashish brings on chronic hashishism, which is much more serious than acute hashishism.

"The countenance of the addict becomes gloomy, his eye is wild, and the expression of his face stupid. He is silent, has no muscular power, suffers from physical ailments, heart troubles, etc.; his intellectual facilities gradually weakens and the entire organism decays. The addict very frequently becomes neurasthenic and eventually insane."

As I promised in my speech, I am venturing to submit to the Conference in as concise a form as possible a memorandum on hashish.

In doing so, I hope that I shall arouse the assembly's interest in this important question.

I do not wish it to be thought, however, that I am only dealing with this question in so far as it concerns Egypt alone. It is true that in our country we have taken the strictest measures against the contraband of this drug, but there are other peoples also which suffer from its ravages. Egypt is not the only nation affected, and I therefore wish to ask you to examine the problem of hashish with all the attention that it deserves, since it is a problem of capital importance for a large number of Eastern peoples.

The *cannabis indica* or *sativa*, called also by the name of hashish (English—Indian hemp; German—indianischer Hanf; French—chanvre indien) was known even in antiquity.

Its cultivation was originally undertaken on the plateau of Persia and Turkestan. Later it was introduced into Asia Minor and Egypt, where it was mentioned by chroniclers of the time of the Crusades. At present the countries which produce it are Siberia, Russia, the Caucasus, Persia, the western plateau of the Himalayas, Kashmir, India and also South eastern Europe.

Researches undertaken with a view to determining the active agent of this plant led to the discovery of a product called cannabine, a kind of soft and brownish resin. An odoriferous oil of an amber color, whose inhalation caused dizziness and giddiness is also derived from *cannabis indica*. In addition, it has been found to contain a certain quantity of nicotine.[1]

[1] See Dictionnaire Encyclopédique des Sciences Médicales by Dechambre and Lereboullet, Paris 1886, Volume XII, pp. 500–516.

The flowers, the tender shoots and the fruits are what are specially utilized in the cannabis. Only the female flowers which have not been fertilized by the male flowers are able to produce the resinous matter, as fertilization destroys the active principle of the plant.

Hashish, prepared in various forms, is used principally in the following ways:

(*a*) In the form of a paste made from the resin obtained from the crushed leaves and flowers, which is cooked with butter and aromatic substances and mixed with sugar, it is used to make sweets, confectionery etc., known in Egypt by the names of manzul, maagun and garawish.

(*b*) Cut into small fragments, it is mixed with tobacco for smoking.

(*c*) The Indian hemp is simply smoked in special hookahs.

We must next consider what are the effects produced by the use of hashish and distinguish between:

(1) Acute hashishism, and

(2) Chronic hashishism.

Acute hashishism occurs when the consumer uses hashish irregularly.

Let us study the effects of this intoxication: Taken in small doses, hashish at first produces an agreeable inebriation, a sensation of well-being and a desire to smile; the mind is stimulated. A slightly stronger dose brings a feeling of oppression and of discomfort. There follows a kind of hilarious and noisy delirium in persons of a cheerful disposition but the delirium takes an extreme form in persons of violent character.

It should be noted that behavior under the influence of the delirium is always related to the character of the individual.

This state of inebriation or delirium is followed by slumber which is usually peaceful but sometimes broken by nightmares. The awakening is not unpleasant; there is a slight feeling of fatigue, but it soon passes." [2]

Hashish absorbed in large doses produces a furious delirium and strong physical agitation: it predisposes to acts of violence and produces a characteristic strident laugh. This condition is followed by a veritable stupor, which cannot be called sleep. Great fatigue is felt on awakening and the feeling of depression may last for several days.

The habitual use of hashish brings on chronic hashishism, which is much more serious than acute hashishism.

The countenance of the addict becomes gloomy, his eye is wild and the expression of his face is stupid. He is silent; has no muscular power; suffers from physical ailments, heart troubles, digestive troubles etc.; his intellectual faculties gradually weaken and the whole organism decays. The addict very frequently becomes neurasthenic and, eventually insane.

In general, the absorption of hashish produces hallucinations, illusions as to time and place, fits of trembling, and convulsions.[3]

A person under the influence of hashish presents symptoms very similar to those of hysteria.[4]

From the therapeutic point of view, science has not made much use of hashish with good results. It has, however, been administered with some success in certain cases of (clinical use) delirium tremens.

Taken thus occasionally and in small doses, hashish perhaps does not offer much danger; but there is always the risk that once a person begins to take it, he will continue. He acquires the habit and becomes addicted to the drug, and once this has happened, it is very difficult to escape. Notwithstanding the humiliations and penalties inflicted on addicts in Egypt, they always return to their vice. They are known as "hashashees" which is a term of reproach with us, and they are regarded as useless derelicts.

Chronic hashishism is extremely serious since hasish is a toxic substance, a poison against which no effective antidote is known. It exercises a sedative and hypnotic effect. It is prescribed in the following doses:

The extract, from 0.015 gr. to 0.06 gr.

The tincture, from 5 to 15 drops.

Generally speaking, hashish is not very much used in medical practice, and its results are a matter of controversy.

In view of the great danger involved by the consumption of hashish, special measures have been taken by the Egyptian Government.

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[2] See Dinet-Sanglé "Action du hachich sur les neurones", Revenue scientifique of March 2nd, 1891.

[3] See Moreau de Tours, Du Hachich et de l'aliénation mentale, Etudes psychologiques.

[4] See Charles Richet, Dictionnaire de Physiologie, Paris, 1909; article by Raymond Mounier, Volume VIII, pp. 188–205).

As early as 1868, Dr. Mohammed Ali Bey, made a report to the competent authorities regarding the accidents caused by the abuse of hashish. In 1884, the cultivation of this plant was forbidden. The cafés (or mashhashes) in which hashish was consumed being smoked in special hookahs, were closed, and are still mercilessly sought out by the police.

Measures were taken to prevent the production and importation of the *cannabis indica;* the following are the chief:

All cultivation of *cannabis indica* is prohibited and the cultivator is liable to a fine of £E.50 (equal to about 26 gold france) per feddau, or fraction of a feddau (the feddau is equal to 4,200.83 square meters).

As regards importation, a few years ago smuggled hashish used to be confiscated and resold to agents for exportation.

At present the goods confiscated are destroyed and a fine of £E.10 per kilogram is imposed on the clandestine importer. However small may be the quantity imported, the fine cannot be lower than £E.2.

It is known, for example, that in a single year (about 1909) more than 140,000 pounds of hashish were consumed in Egypt.[5]

Some ideas of the ravages produced by these enormous quantities of hashish clandestinely consumed may be gained from the fact that the real requirements of the country hardly ever exceed 50 kilograms annually.

For example, the requirements of hashish for medical purposes in an average year may be estimated at 11,165 kilos of extract; 1,331 kilos of soft extract; and 12,375 kilos of tincture.

In 1919, the Egyptian Government allowed the importation of 65 kilos of hashish for medical purposes and in 1920 of 23 kilos.

The illicit use of hashish is the principal cause of most of the cases of insanity occurring in Egypt. In support of this contention, it may be observed that there are three times as many cases of mental alienation among men as among women, and it is an established fact that men are much more addicted to hashish than women. (In Europe, on the contrary it is significant that a greater proportion of cases of insanity occur among women than among men.)

Generally speaking, the proportion on cases of insanity caused by the use of hashish varies from 30 to 60% of the total number of cases occurring in Egypt.

My Government is giving increasing attention to finding the best method of eradicating this social evil. Other countries are also taking an interest in this question. In the English House of Commons on February 19th, 1924, for example Mr. Gilbert asked the Government a question regarding hashish and its uses. He expressed surprise that hashish was not included in the list of dangerous drugs which were under restriction of importation into Great Britain. He asked whether the Government had any information of the use of the drug in certain seaport towns, and whether it proposed to take any steps to add this drug to the list of dangerous drugs and place it under the same restrictions as applied to them.

Mr. Rhys Davies replied that indulgence in the use of hashish was rare in Great Britain, though it was possible that it was practiced to a certain extent among oriental seamen visiting her ports.

Hashish was not one of the drugs to which the International Opium Convention of 1912 applied, though the Hague Conference recommended that its use should be investigated. Any proposal for the extension to hashish of the restrictions relating to the drugs included in the Convention would have to be considered from the international standpoint.

He understood that the League of Nations, which by the Treaty of Peace was entrusted with the general supervision over the traffic in dangerous drugs, had not yet considered the question.

He added, "the question is one in which other countries are more closely concerned than this country, but the position is being watched by my department, and, if it appears desirable, steps will be taken to raise the question before the Opium Advisory Committee of the League."[6]

I was very glad to hear that the South African Government had made the same proposal as myself. I would also specially like to thank the honorable delegates of the United States, Turkey, Japan, Brazil, Poland, Greece and other countries, who have assured me that this subject was also comprised in their

[5] "Dictionnaire de Physiologie" by Ch. Richet, Paris 1909. Article by Raymond Mounier, Vol. VIII. Pages 188–200.

[6] See the Lancet of March 1st, 1924, pp. 469–470.

programs. And I would like to thank all the delegates to whom I have spoken on this question and who have promised me their support.

I do not see why we should wait until 1925 to take a decision on this question, since a large number of countries, have pronounced in favor of my proposal through their delegates.

Personally, even at the risk of seeming importunate, I insist and will continue to insist on the importance of this question, being confident that in this respect I am voicing the views of the entire Egyptian people, from His Majesty King Fuad I, our august and well-beloved sovereign, who takes a special interest in the question, down to the humblest fellah of the Nile valley.

I earnestly beg all the delegates to give this question their best attention, for I know the mentality of oriental peoples, and I am afraid that it will be said that the question was not dealt with because it did not affect the safety of Europeans. I am in full agreement with my eminent colleague Dr. Chodzko, who said that considerations of religion, of race or of nationality must not ever be allowed to stand in the way of the humanitarian work which the League of Nations undertakes.

Moreover, I am sure that if we take a decision regarding opium and the drugs mentioned in the schedule of the Advisory Committee without adding hashish, the latter will soon replace the other narcotics and will then become a terrible menace to the whole world.

The League of Nations aims at safeguarding the liberty of man. It is an arbiter guaranteeing the rights of every nation.

The League wants all the citizens of the world to be able to live their lives in freedom and good health, and therefore I am sure that it will give its attention to the havoc wrought by hashish among our population.

It will save the thousands of human beings who lose their reason every year as a consequence of excessive use of hashish.

The League of Nations will earn the gratitude of all those it will have rescued from the hashish habit, and it will thus swell the ranks of those who wish to fight under its banner in the good cause.

Let the League of Nations help us then in the struggle we have undertaken against this scourge, which reduces man to the level of the brute and deprives him of health and reason, self-control and honor.

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[From JAMA, Apr. 19, 1971]

## Effects of Marihuana on Adolescents and Young Adults

(By Harold Kolansky, MD, and William T. Moore, MD)

*Editorial Summary*

1. In animal experiments, there is a marked diminution of oxygen intake by the brain while the animals are intoxicated with marihuana.

2. "Most of the patients in this study smoked marihuana two or more times weekly and, in general, smoked two or more marihuana cigarettes each time. These patients consistently showed very poor social judgment, poor attention span, poor concentration, confusion, anxiety, depression, apathy, passivity, indifference, and often, slowed and slurred speech. An alternation of consciousness which included a split between an observing and an experiencing portion of the ego, an inability to bring thoughts together, a paranoid suspiciousness of others, and a regression to a more infantile state, were all very common. Sexual promiscuity was frequent, and the incidence of unwanted pregnancies among female patients was high, as was the incidence of venereal disease. This grouping of symptoms was absent prior to the onset of marihuana smoking, except in 11 patients. . . ."

3. "Clearly there is, in our patients, a demonstration of an interruption of normal psychological adolescent growth processes following the use of marihuana; as a consequence, the adolescent may reach chronological adulthood without achieving adult mental functioning or emotional responsiveness."

[From the Child Analysis Division, Philadelphia Association of Psychoanalysis (Drs. Kolansky and Moore), and Hahnemann Medical College of Philadelphia (Dr. Moore).]

Reprint requests to 7900 Old York Rd, Elkins Park, Pa 19117 (Dr. Kolansky).

The large amount of marihuana smoking (12 million to 20 million people) in this country was reviewed, as well as some of the literature concerning adverse effects. Thirty-eight individuals from age 13 to 24 years, all of whom smoked marihuana two or more times weekly, were seen by us between 1965 and 1970, and all showed adverse psychological effects. Some also showed neurologic signs and symptoms. Of the 20 male and 18 female individuals seen, there were eight with psychoses; four of these attempted suicide. Included in these cases are 13 unmarried female patients who became sexually promiscuous while using marihuana, seven of these became pregnant.

The smoking of cannabis derivatives in the United States has now reached alarming proportions. Between 12 million (estimated by J. L. Goddard, MD, U.S. Food and Drug Administration, in *Life*, Oct. 31, 1969, p 34) and 20 million (estimated in *Drug Abuse: The Chemical Cop-Out*, National Association of Blue Shield Plans, 1969) adolescents and young adults are using, or have tried smoking, cannabis derivatives. In February 1970, a *Newsweek* survey (Feb. 16, 1970, p 65) showed that 30% to 50% of all high-school students in this country had made marihuana an accepted part of life. Results of surveys of college students smoking marihuana are similarly high. In our own observations at local high schools and at several college campuses along the eastern seaboard, we have noted the openness of marihuana smoking, which may indicate a trend toward more universal use of the drug. All of this is in marked contrast to the situation as recently as four years ago when the COMMITTEE ON ALCOHOLISM and DRUG DEPENDENCE of the American Medical Association reported that most experimenters give up the drug quickly or continue to use it on a casual basis.[1]

Literature in the United States describing the adverse effects of smoking marihuana is rather sparse. Among the more important communications was a report by Bromberg[2] in 1934, describing studies made while individuals smoked. Talbott and Teague[3] recently described 12 patients with acute toxic psychosis associated with cannabis smoking. Of special significance in their communication was the development of psychosis in each of the 12 upon the first smoking of marihuana. Ten of 12 were delusional, and all showed paranoid symptoms. Physical symptoms, including evidence of neurologic dysfunction, were seen in some. Ten showed no history of premorbid personality disorder. The American Medical Association's COUNCIL ON MENTAL HEALTH, along with the National Research Council of the National Academy of Science,[4] and an editorial in THE JOURNAL in 1968[5] warned that cannabis is a dangerous drug and a public health concern. Also, there have been articles by Ames[6] and Allentuck[7] describing ill effects.

In the literature of clinical experiments, Isbell[8] and his associates showed that the isolated chemically-active ingredient of the cannabis group, (—) -$^9$-*trans*-tetrahydrocannabinol, caused psychotic reactions in humans tested at the Addic-

[1] Dependence on cannabis (marihuana), Committee on Alcoholism and Drug Dependence, and Council on Mental Health, JAMA 201:368–371, 1967.

[2] Bromberg W.: Marihuana intoxication: Clinical study of *Cannabis sativa intoxication*. *Amer. J. Psychiat.* 91: 303–330, 1934.

[3] Talbott J. A., Teague, J. W.: Marihuana psychosis. JAMA 210:299–302, 1969.

[4] Marihuana and society, Council on Mental Health. JAMA 204:1181–1182, 1968.

[5] Marihuana thing, editorial. JAMA 204:1187–1188, 1968.

[6] Ames F.: A clinical and metabolic study of acute intoxication with *Cannabis sativa* and its role in the model psychosis. *J. Ment. Sci.* 104:972–999, 1958.

[7] Allentuck S.: Medical aspects, in *The Marijuana Problem in the City of New York, 1941*, reprinted in Solomon D (ed.): *The Marijuana Papers*, New York, Bobbs-Merrill Co., Inc., 1966, pp. 269–284.

[8] Isbell H., Gorodetzky C. W., Jasinski D., et al. Effects of (—) $\Delta^9$ trans-tetrahydrocannabinol in man. *Psychopharmacologia* 11: 184–188, 1967.

tion Research Center in Lexington, Ky. Hartmann [9] and Wieder and Kaplan [10] described some psychological effects in 1969.

In the pharmacological literature, a detailed report and review by Gershon [11] in 1970 showed the many effects of marihuana on animals. He stressed that, in most animals extracts of marihuana induced stimulation and excitement followed by general depression. Gershon also called our attention to the marked diminution of oxygen uptake by the brain while the animals were intoxicated with marihuana.

We (both authors) are in separate, individual, private practices of child and adult psychiatry and psychoanalysis, and both of us have extensive consultative opportunities. In the period from 1965 to 1970, we began to note a sizeable increase in referrals of individuals who, upon investigation by history, showed an onset of psychiatric problems shortly after the beginning of marihuana smoking; these individuals had either no premorbid psychiatric history or bad premorbid psychiatric symptoms which were extremely mild or almost unnoticeable in contrast to the serious symptomatology which followed the known onset of marihuana smoking. In our study, all in this group who smoked marihuana more than a few times showed serious psychological effects, sometimes complicated by neurologic signs and symptoms. In 38 of our patients, our findings demonstrate effects ranging from mild to severe ego decompensations (the latter represent psychoses).

Simultaneously, we have examined and treated many other marihuana smokers who either had severe psychological problems prior to smoking marihuana or who also used lysergic acid diethylamide (LSD), the amphetamines, or other drugs; these patients had more complex findings and were not included in this study of 38 patients because we could not be certain that symptoms seen were related to marihuana alone. We have studied some neurotic individuals whose symptoms became more severe after smoking marihuana, but since their earlier symptomatology would becloud such a study as this, we did not include them. Still others who had a marked predisposition to psychosis and who became psychotic after beginning to smoke marihuana were not included in this series, since our purpose was to report only the effects seen as a consequence of marihuana smoking in those not showing a predisposition to serious psychiatric problems. We are currently studying the group with a known predisposition to determine whether marihuana acted as a catalyst to produce psychosis. The 38 patients described in this communication range in age from 13 to 24 years, and the group consists of 20 male and 18 female individuals. We have seen many patients older than 24 who have been smoking marihuana and who have similar symptoms to those we describe, but we have confined our present communication to those aged 24 and younger.

## METHODS

Prior to 1965, we only occasionally saw patients who smoked marihuana. The 38 patients described are part of a consultation practice that included several hundred new referrals seen during the five-year period from 1965 to 1970, most of whom did not smoke marihuana.

To establish a diagnosis for the usual adult referred for consultation, we see the patient once or twice to determine his history and to examine his psychiatric status; following this, treatment recommendations are made. When children and adolescents are referred, we see the parents two to five times to obtain a history; following this we examine the youngsters in one or two office visits. About one of four of our patients is also psychologically tested. Psychological testing is performed by clinical psychologists with long experience on those of our patients for whom our diagnostic impressions are that we are dealing with a psychosis, an ego disturbance, an organic central nervous system disorder, or a severe learning disability. We followed the same diagnostic procedures with those of our patients known to be smoking marihuana.

Formal neurologic examinations were not done, but there were gross indications of neurologic impairment in a few patients who smoked marihuana four or

[9] Hartmann, D.: A study of drug-taking adolescents, in Eissler S., Freud, A., Hartmann, H., et al (eds.): *The Psychoanalytic Study of the Child.* New York, International Universities Press, Inc., 1969, vol. 24, pp. 384–398.

[10] Wieder H., Kaplan, E. H.: Drug use in adolescents: Psychodynamic meaning and pharmacogenic effect, in Eissler S., Freud, A., Hartmann, H., et al (eds.) *The Psychoanalytic Study of the Child.* New York, International Universities Press, Inc., 1969, vol. 24, pp. 399–431.

[11] Gershon S.: On the pharmacology of marihuana, *Behav. Neuropsychiat.* 1 :9–18, 1970.

five times weekly for many months. This impairment consisted of slurred speech, staggering gait, hand tremors, thought disorders, and disturbance in depth perception (such as overshooting exits on turnpikes, misjudging traffic lights and stop signs at intersections, diminished ability to time catching a baseball, or undershooting a basketball net).

A diagnosis was established and treatment recommendations were made for each of our 38 patients. In some, psychotherapy or psychoanalysis was indicated, and in that group, further psychological understanding of the underlying causes of marihuana smoking was obtained. In others, the gamut of psychiatric treatment was instituted, which sometimes, of necessity, included hospitalization.

In each instance, only one of us diagnosed the condition and prescribed the treatment. In a few instances, diagnosis was made by one author and treatment was instituted by the other. In these few cases, there was agreement on diagnosis.

### GENERAL PSYCHIATRIC CONSIDERATIONS

Most of the 38 patients in this study smoked marihuana two or more times weekly and, in general, smoked two or more marihuana cigarettes each time. These patients consistently showed very poor social judgment, poor attention span, poor concentration, confusion, anxiety, depression, apathy, passivity, indifference, and often, slowed and slurred speech. An alteration of consciousness which included a split between an observing and an experiencing portion of the ego, an inability to bring thoughts together, a paranoid suspiciousness of others, and a regression to a more infantile state were all very common. Sexual promiscuity was frequent, and the incidence of unwanted pregnancies among female patients was high, as was the incidence of venereal diseases. This grouping of symptoms was absent prior to the onset of marihuana use, except in 11 patients who were conscious of mild anxiety or occasional depression.

There was marked interference with personal cleanliness, grooming, dressing, and study habits or work or both. These latter characteristics were at times present in some patients prior to smoking marihuana, but were always markedly accentuated following the onset of smoking. In one subgroup, a clear-cut diagnosis of psychosis was established, and in these patients, there was neither evidence of psychosis or ego disturbance nor family history of psychosis prior to the patients' use of marihuana. Several in this group were suicidal. In some individuals, instead of apathy, hyperactivity, aggressiveness, and a type of agitation were common. In no instance were these symptoms in evidence prior to the use of marihuana.

### A. PSYCHOSIS WITH SUICIDAL ATTEMPTS

Four individuals, two male and two female between the ages of 14 and 17, showed psychotic reactions directly attributable to cannabi derivatives, and each attempted suicide. In the usual type of adolescent psychosis, there is an antecedent history of very poor ego organization. In no instance was there a history of such earlier ego disorganization in our eight psychotic patients; nor prior to smoking marihuana was there psychosis, ego disturbance, family history of psychosis, fragile ego, or suicidal attempts.

CASE 1.—A 17-year-old girl smoked marihuana daily for one year prior to consultation and for an additional year while she was in psychiatric treatment. By history from her parents and by observation during the year following entry into treatment, she showed a gradual regression in organizing thought. She continuously repeated phrases and had the delusion that she was a great actress, but saw life as through a veil. Speech and thinking slowed down, and she believed that she was living life in slow motion. Memory and perception became markedly impaired, thinking became tangential, and judgment became poor. This led to marked social and familial difficulties. Suicide was attempted while she was smoking marihuana, and despite the seriousness of the attempt, the patient was euphoric during and following the effort, with slurred speech, pleasant mood, absent judgment, and missing reality testing.

CASE 2.—A 17-year-old boy was seduced homosexually after an older man gradually introduced him to marihuana smoking over a period of one year. His history showed no evident previous psychopathological condition, and his adolescent development appeared to be normal prior to smoking. Confusion and depression gradually developed, which led to psychiatric evaluation. He continued to smoke marihuana and gradually withdrew from reality, developing an interest in occult matters which culminated in the delusion that he was to be the Messiah returned to earth. He attempted suicide three times by wrist cutting. When he

was hospitalized and marihuana was withdrawn, a slow and gradual reversal of the process described occurred.

CASE 3.—Shortly after a 14-year-old boy began to smoke marihuana, he began to demonstrate indolence, apathy, and depression. Over a period of eight months, his condition worsened until he began to hallucinate and to develop paranoid ideas. Simultaneously, he became actively homosexual. There was no evidence of psychiatric illness prior to smoking marihuana and hashish. At the height of his paranoid delusions, he attempted suicide by jumping from a moving car he had stolen. He was arrested, and during his probation period, he stopped smoking and his paranoid ideation disappeared. In two six-month follow-up examinations, he was still showing some memory impairment and difficulty in concentration. Of note was the fact that he still complained of an alteration in time sense and distortion of depth perception at the time of his most recent examination.

CASE 4.—A 16-year-old girl in whom there was no prior psychiatric difficulty smoked cannabis derivatives (marihuana and hashish) at first occasionally, and then three to four times weekly for a period of two years. She began to lose interest in academic work and became preoccupied with political issues. From a quiet and socially popular girl, she became hostile and quite impulsive in her inappropriate verbal attacks on teachers and peers. She dropped out of school in her senior year of high school, which led to psychiatric referral. She showed inappropriate effect and developed paranoid ideas about an older sister's husband having sexual interests in her. She refused to give up smoking marihuana and eventually became so depressed that she attempted suicide by hanging. After withdrawal from the drug, her depression and paranoid ideas slowly disappeared, as did her outbursts of aggression. Ten months of follow-up showed continued impairment of memory and thought disorder, marked by her complaint that she could not concentrate on her studies and could not transform her thoughts into either written or spoken words as she had once been able to do quite easily.

### B. PSYCHOSES WITHOUT SUICIDAL ATTEMPTS

Four individuals, all male between the ages of 18 and 24, showed psychoses as a consequence of smoking cannabis derivatives. As with those who attempted suicide, this group showed no prior history of ego fragility, predisposition to psychosis, or familial history of psychosis.

CASE 1.—A married 24-year-old man who had shown no previous psychiatric illness or evidence of personality disorder met a group of new friends who taught him to smoke marihuana. He enjoyed the experience so much that he smoked it daily for two months, claiming that it did not interfere with his daily functioning. He even said that he could think more clearly. Gradually he began to withdraw from his friends and seemed suspicious of them. He developed ideas of reference, believing that his friends talked about him saying that he was impotent. (Impotence had actually occurred on several occasions after he had smoked a large amount of "good hash.") He also believed that he was developing heart disease as a result of "bad drugs." He had experienced palpitations and a feeling of his heart "jumping" in his throat on several occasions while smoking some Mexican marihuana. He believed that his friends were trying to do away with him in order to have his wife. At the end of the two months, he showed a full-blown paranoid psychosis and had delusions of grandeur. He believed that he had developed a superior intellect at the expense of a loss of his sexual life. He was the first member of a new "super race." After stopping his smoking, his delusional ideas disappeared and he returned to his normal functioning in his job and marriage.

This patient and the others in this subgroup, although delusional, were never hospitalized, since they adequately functioned in other ways. It was only after some acquaintance with the psychiatrist that each of these patients told of his delusional system. Characteristic of some of our long-term marihuana smokers who developed paranoid delusions is an ability to function for a period of time without others being aware of their illness, either because they join groups who share their aberrational thinking or because they keep their delusional thoughts to themselves.

We have also noted that, as these individuals withdraw from marihuana, the delusional system is given up more quickly in those patients who have been smoking for a shorter period of time; however, as better reality testing is achieved, these patients seem to be left with a residual of some memory difficulty and impairment of concentration. One patient has shown this for two years at the time of this writing.

CASE 2.—A 20-year-old man developed delusions of omnipotence and grandeur six months after starting to smoke marihuana. He believed that he was in charge of the Mafia and that he was an Eastern potentate of the Ku Klux Klan. He began to collect guns and knives in addition to training his German shepherd dog to attack others. He had not previously smoked marihuana except experimentally on two occasions while in college. He graduated cum laude in business administration in less than three years by attending summer school. He worked in a family business and was doing creditably in his job as well as in his social life. He found his way into a "swinging" crowd that smoked cannabis derivatives regularly. He took up "the habit" and almost immediately noticed changes in his working pattern and a shift or decline in ambition. He gradually withdrew from a heterosexual relationship after a few episodes of impotence while "high" on hashish. He became apathetic and more of a "loner," and then finally became distrustful of his friends and family. At this point, he sought psychiatric treatment and told of his delusional thoughts, fearful that he was losing his mind. Upon withdrawal from the drug, psychotic symptoms disappeared, yet a residual of difficulty in thinking (which he described as "fuzzy") was still complained of in a one-year follow-up examination.

CASE 3.—An 18-year-old boy who smoked marihuana and hashish regularly for a three-year period became progressively withdrawn, confused, and depressed. His interest in astrology and Eastern religions increased. He became a vegetarian and practiced yoga. He had the delusion that he was a guru and eventually believed that he was the son of God who was placed on earth to save all people from violence and destruction. This patient gave a history of mild anxiety and headaches in his earlier adolescent years, as well as that of some difficulty in getting along with others. Prior to smoking marihuana, he had mild general and social anxiety and headaches for several years. He began smoking marihuana occasionally with friends at the age of 15, and over a two-year period, showed signs of ego decompensation. He did poorly in school, although he could "get along." When he increased the frequency of smoking, delusional symptoms began to develop. Consultation with one of us previously because of some of his adolescent difficulties made it easier for him to consult us again upon becoming concerned with his beliefs that he was God's son. He knew that his thoughts were not "right" and worried when a smoking friend told him of his own similar delusions. There was even a joke among his crowd that they knew "a guy had gone too far" when he thought that he was like a god. Persuasion could not convince this young man to give up cannabis, although he acknowledged that his symptoms resulted from drug use. After consultation, he moved to the west coast and continued his unproductive, aimless life, supported financially by his parents.

CASE 4.—A 19-year-old boy smoked marihuana for four months, gradually developing ideas of reference. Believing he had superhuman mental powers, he felt that he was able to communicate with and control the minds and actions of animals, especially dogs and cats. No one knew of his belief in his messianic powers and divine rights. He was referred for psychiatric consultation by his school because of a sharp decrease in his interest in his schoolwork. He seemed listless, apathetic, and depressed. Prior to smoking marihuana he had been outgoing and did well academically, but following the onset of smoking he shunned family and friends. He continued to maintain good grades on the basis of sheer momentum of accumulated academic experience, although there was decline in academic interest.

His most closely guarded secret was the belief that he was the Messiah, and although he believed this to be a "weird idea," he felt it to be true and thought that marihuana gave him this power.

Upon cessation of marihuana smoking, the delusional system disappeared, and he was able to return to a level of functioning similar to that of the days before marihuana smoking.

It was our impression in these cases that the use of cannabis derivatives caused such severe decompensation of the ego that it became necessary for the ego to develop a delusional system in an attempt to restore a new form of reality. It would appear that this type of paranoid reaction is a direct result of the toxic effects of cannabis upon the ego organization of those patients described in this study.

We have not included in this communication a large number of cases of psychosis due to the use of other psychotomimetric drugs in combination with cannabis derivatives. It is our impression that those patients who had been taking LSD or mescaline or both with marihuana appeared to have more acute psychotic reactions which were accompanied by greater panic and distress, resulting in more frequent need for hospitalization, than those smoking marihuana alone.

C. BORDERLINE STATES (EGO DECOMPENSATION) IN THOSE ON TRIAL FOR POSSESSION OF MARIHUANA

Twelve adolescents (aged 15 to 18), nine male and three female, had smoked marihuana regularly for one or more years prior to being arrested for using marihuana. In each instance, the legal authorities asked for a psychiatric evaluation, and none of these individuals smoked marihuana immediately prior to the examination. All 12 showed evidence of ego decompensation and disturbance in reality testing, memory, social judgment, time sense, concept formation, concentration, abstract thinking, and speech production. All 12 gave a history of steadily declining academic ability and class standing, and all felt isolated from others. Eight of this group complained of trouble converting thoughts into words, which resulted in a rambling, disjointed flow of speech with hesitation and circumstantiality. Memorized phrases were frequently substituted to mask the loss of speech and thought continuity.

Three of these adolescents had periods of depersonalization while *not* under the influence of the drug. They felt that they were watching themselves and others interreact, as if in a dream.

None of these 12 individuals showed evidence by history of psychotic disturbance prior to beginning to smoke marihuana.

Psychological testing performed on four patients in this group showed these patients to have regressed to early stages of psychological development and to be relying on omnipotent and grandiose fantasies as methods of psychological defense against anxiety. All of these patients showed impairment in control of impulses and judgment and an inability to distinguish the subleties of the feelings of others in social situations. Limited attention span and encroachment on reality testing, as well as generally impaired cognition, were evident in all.

The psychological tests were done without the psychologists' previous knowledge of cannabis use by the patients, but testing was not used to help determine whether cannabis was used or whether cannabis produced a specific effect. It was used instead to help determine the extent of ego decompensation.

A bright 16-year-old boy smoked marihuana for 18 months. He had a "B" average prior to smoking. He was well liked by teachers and peers, seemed happy, and appeared to have no more difficulties than other adolescents prior to smoking marihuana. He said that he began to smoke because his friends did. He felt that it was safe, believing marihuana was harmless. As he began to notice some apathy, loss of goal direction, and increasing depression, he still felt that marihuana was not harmful.

Upon examination, he attempted to win over the psychiatrist with a pleasant, willing, cooperative manner. There was, however, mild disorientation, feelings of omnipotence, and a feeling of isolation.

In psychological testing, he had bright-normal scores in the Wechsler-Bellevue intelligence scale. He showed poor attention span and concentration and poor retention of acquired, as well as of accumulated, knowledge. There was evidence of tenuous control of impulses. Reality testing was impaired. The psychologist reported "early signs of personality decompensation in that he retreated into himself. He functioned at a level of early childhood, believing in his own omnipotence. This state might result in further impulse-motivated behavior so that he would probably commit further asocial and/or anti-social acts prior to becoming severely depressed."

D. BORDERLINE STATES (EGO DECOMPENSATION) NOT AT FIRST ASSOCIATED WITH MARIHUANA

Six individuals 14 to 20 years of age, five male and one female, were seen in consultation. All of these individuals were seen because of the chief complaints of general deterioration in schoolwork, inability to concentrate or to pay attention in class, gradual decrease in academic standing, apathy, indifference, passivity, withdrawal from social activities, and limitation of interest. All showed the same evidence of ego decompensation as described in group C, including disturbance in reality testing, memory, social judgment, time sense, concept formation, concentration, abstract thinking, and speech production. All felt isolated from others. Four of these individuals showed no prior history of these symptoms, while two showed some difficulty in concentration in school prior to smoking marihuana. In the latter two, the difficulty in concentration became far more pronounced following regular smoking of marihuana.

CASE 1.—A 19-year-old college freshman arrived on time for psychiatric consultation, dressed in old, torn, dirty clothes. He was unkempt, with long hair that was uncombed and disheveled. He talked in a slow, hesitant manner, frequently losing his train of thought, and he could not pay attention or concentrate. He tried hard to both talk and listen, but had difficulty with both. He had been an excellent high-school athlete and the brightest student in his class in a large city. He was described as neat, orderly, and taking pride in his appearance, intellect, and physical fitness. During the last half of his senior year, he began casual (one or two marihuana cigarettes each weekend) smoking. By the time of the evaluation in the middle of his first college year, he was smoking several marihuana cigarettes daily. While in college, he stopped attending classes, didn't know what his goals were, and was flunking all subjects. He partook in no athletic or social events, and was planning to drop out of college to live in a young, drug-oriented group.

CASE 2.—A 19-year-old boy entered college with an "A" average. He began smoking marihuana early in the freshman year, and within two months of starting to smoke cannabis, he became apathetic, disoriented, and depressed. At the semester's end, he had failed all courses and lacked judgment in most other matters. Upon return to his home, he discontinued marihuana after a total period of 3½ months of smoking. Gradually, his apathy disappeared, his motivation returned, and his personal appearance improved. He found employment, and in the following academic year, he enrolled at a different university as a preprofessional student. His motivation returned, as did his capability. As with so many of our patients, this young man told his psychiatrist that he had observed changes while smoking marihuana; he even went to a college counselor and told the counselor that he felt he was having a thinking problem due to smoking marihuana. The counselor reassured him that the drug was harmless and that there was no medical evidence of difficulties as a consequence of smoking.

### E. EGO IMPAIRMENT WITH MARKED SEXUAL PROMISCUITY

Thirteen female individuals, all unmarried and ranging in age from 13 to 22, were seen in consultation with almost the same symptoms as those in groups C and D. (One in this group was psychotic and is listed as case 1 of group A. Thus, our total reported group of cases remains 38, not 39.)

This group is singled out because of the unusual degree of sexual promiscuity, which ranged from sexual relations with several individuals of the opposite sex to relations with individuals of the same sex, individuals of both sexes on the same evening. In the histories of all of these individuals, we were struck by the loss of sexual inhibitions after short periods of marihuana smoking. Seven patients of this group became pregnant (one on several occasions), and four developed venereal diseases. Each showed confusion, apathy, depression, suicidal ideas, inappropriateness of affect, listlessness, feelings of isolation, and disturbances in reality testing, and among the 13, all of whom attended junior high school, high school, or college, all showed a marked drop in academic performance. The decline in academic performance was in direct proportion to the frequency and amount of smoking. Most smoked three or more times weekly.

Five of the 13 were engaged in homosexual activities which began after the onset of smoking, and three attempted suicide.

In no instance was the sexual promiscuity prior to the beginning of marihuana smoking, and in only two of the 13 cases were there histories of mild anxiety states prior to smoking. We take these results to indicate marihuana's effect on loosening the superego controls and altering superego ideals.

### ADOLESCENT DEVELOPMENT AND MARIHUANA

The nature of adolescent development is of importance in a discussion of marihuana. The adolescent may begin to smoke marihuana and then suffer damage in further psychological growth, development, and maturation.

In brief, adolescence has as its central driving force the organic, maturational establishment of puberty. Related to physical changes of adolescence are profound (normal) psychological and changes.

Anna Freud[12] has described these psychological changes in the normal adolescent as follows:

It is normal for the adolescent to behave . . . in an inconsistent and unpre-

[12] Freud, A.: Adolescence, in Eissler, S., Freud, A., Hartmann, H., et al (eds.): *The Psychoanalytic Study of the Child,* New York, International Universities Press, Inc., 1958, vol. 16, pp. 255–278.

dictable manner; to fight his impulses and to accept them; . . . to love his parents and to hate them; . . . to thrive on imitation of and identification with others while searching unceasingly for his own identity; to be more idealistic, artistic, generous, and unselfish than he will ever be again; but also the opposite, self centered, egoistic and calculating.

These psychological changes, according to Pearson,[13] are due to the unsettling effect of sudden, general bodily growth and the gradual changes in primary and secondary sexual characteristics, as well as to a final stage of myelinization within brain tracts which leads to greater perception of nuances of color and sound. Pearson also described the conflict of generations, and how lack of parental understanding further weakens the adolescent's ego, leading to the psychological changes already mentioned.

The normally developing adolescent compares the image of his body (often characterized by uneven growth spurts) to his preadolescent body (smooth and even), to those of his peers (different), and to those of adults (who are ambivalently admired), and feels himself lacking. He is bombarded by known sexual impulses related to the organic sexual changes, and he feels overwhelmed and at first unable to control or deal with these impulses effectively. He feels flooded by subtleties of color and sound never before perceived, but now very taxing to his mind. Typically, in efforts at management of these biologically induced phenomena, and also due to the struggle with his parents, he regresses psychologically and tends to handle these anxieties in paradoxical ways, as by immersing himself in glaring colors and loud sounds, by fighting with parents, or by dressing in a bizarre way which accentuates his body-growth disproportions.

The normal adolescent needs support and guided firmness from the parent. If this is missing, he may turn increasingly to drugs. The adolescent living in a ghetto has the added problem of the absence of daily necessities, making reality harsh and the appeal of drugs even stronger. When the adolescent is further exposed to equivocation by authorities in speech or writing on the innocence of dangers of marihuana, then his urge toward a drug solution for conflict may be enhanced, and if there has been a lack of support and interest in the child prior to adolescence and a lack of continuing interest, support, and benevolent firmness by the parent in the teen-age years, the adolescent may still more readily turn to drugs.

To illustrate the issue of lack of firm guidance, several of our patients had parents who talked to the adolescent of their own curiosity about the effects of marihuana, without emphasizing its dangers, or emphasized the discrepancies in the law, without insisting that the youngster must not use marihuana or other drugs because of the serious effects that would occur. We have found that equivocation by the parents has contributed to eventual drug experimentation.

Most often, the normal adolescent, weakened by his own changes, and disillusionment with parental ideals, seeks peer relationships to establish new ideals and thereby strengthen his own character. Among his peers today, he finds many smoking marihuana. He cannot tolerate the isolation from those who smoke. Also, the need to repudiate parental ideals is strong. In his desperation to find new ideals, he turns to those who use drugs. Even though their smoking frightens him, gradually he accepts their drug use. He cannot see any changes in his friends as a result of smoking cannabis (early changes are even difficult for the professional to detect). He identifies, however, with their rebellious attitude toward authority as expressed by their use of marihuana. He may then smoke. At first, he is puzzled and disappointed at not reaching a "high" (which he will not admit to his new friends), and he fails to see any adverse effect upon himself other than some exaggeration or distortion of sensory perceptions. He continues to smoke in an attempt to achieve an effect. His parents and others are thought to be alarmists; he can see no harm in "smoking a little pot." He is unaware that increased smoking over a period of time will likely deprive him of the ability to adequately resolve his internal conflicts.

When we examined the effects of marihuana on the adolescents in our study, we were struck by the accentuation of the very aspects of disturbing bodily development and psychological conflicts which the adolescent had been struggling to master. Marihuana accentuates the inconsistencies of behavior, the lack of control of impulses, the vagueness of thinking, and the uncertainty of body

[13] Pearson G. H. J.: *Adolescence and the Conflict of Generations.* W. W. Norton & Co., Inc., 1958, pp. 1–186.

identity which Anna Freud described. Moreover, dependency and passivity are enhanced at a time when the more natural course would be to master dependent yearnings and to become independent. Rebellion toward parents and authority is increased while the adolescent is struggling toward abandoning such rebellion. His uncertainty about sex grows while he smokes marihuana. The desire to be independent diminishes while he is smoking with his peers.

While the adolescent is struggling to master his feelings about bodily growth surges, he is confronted with further changes in the mental image of his body if smoking marihuana. Also, while he is struggling to master new physical, intellectual, and emotional strengths, he is hampered by marihuana. This leads to further anxiety.

Moreover, while struggling to make order out of the sudden flood of new sounds and colors incident to normal brain maturation, he is inundated by the changes in sensory perceptions which are the hallmark of marihuana use. While valuing clear thinking, coherent speech, alertness of reasoning, good attention span, and concentration, he is now confronted with at least temporary interference with these activities.

Our study showed no evidence of a predisposition to mental illness in these patients prior to the development of psychopathologic symptoms once moderate-to-heavy use of cannabis derivatives had begun. It is our impression that our study demonstrates the possibility that moderate-to-heavy use of marihuana in adolescents and young people without predisposition to psychotic illness may lead to ego decompensation ranging from mild ego disturbance to psychosis.

Clearly, there is, in our patients, a demonstration of an interruption of normal psychological adolescent growth processes following the use of marihuana; as a consequence, the adolescent may reach chronological adulthood without achieving adult mental functioning or emotional responsiveness.

We are aware that claims are made that large numbers of adolescents and young adults smoke marihuana regularly without developing symptoms or changes in academic study, but since these claims are made without the necessary accompaniment of thorough psychiatric study of each individual, they remain unsupported by scientific evidence. No judgment on the lack of development of symptoms in large, unselected populations of students or others who smoke marihuana can be made without such definitive individual psychiatric history-taking and examination.

[From British Journal of Addiction, 1966]

CANNABIS—A TOXIC AND DANGEROUS SUBSTANCE—A STUDY OF EIGHTY TAKERS

(By P. A. L. Chapple, Assistant Psychiatrist, West Park Hospital Epsom)

*Editorial summary*

1. "This paper is a retrospective study of 80 heroin and cocaine addicts reviewing a previous phase of their drug-taking . . . it became clear that although they talked of a number of other drugs, their attitude toward cannabis was quite different from their attitude toward these other drugs. They were quite unprepared to say that they would give up smoking cannabis, even if their opiate addiction were cured. Moreover, they talked of cannabis in terms of great enthusiasm, and in general they were agreed . . . that it wasn't a 'drug of addiction.'"

2. "Most addicts agree that this is a social drug, and smoke it together at parties, either employing individual cigarettes or a communal cigarette. This may be passed around the gathering, being taken in turns, each person taking a puff. This method ensures the participation of those who have not previously taken the drug."

> 3. "Time of onset of effect (of marihuana) seems variable: Some people say they obtain a 'kick' from the first smoke. Others say that they have to take it for some time before they were affected; for several months before they really get a 'kick.' Presumably they were 'social smokers' during the intervening phase. . . . Sooner or later there is a great effect. . . . The users at some stage become 'stoned' or 'blocked'. . . . Various combinations of the drug with heroin are described by habitues, such as 'I needed heroin to bring me down.' "

This paper is a retrospective study of 80 heroin and cocaine addicts, reviewing a previous phase of their drug taking. During a study of opiate addicts, inquiries were made of their preceding drugs: it became clear that though they talked of a number of other drugs, their attitude towards cannabis was quite different from their attitude towards these other drugs. They were quite unprepared to say that they would give up smoking cannabis, even if their opiate addiction were cured; moreover, they talked of cannabis in terms of great enthusiasm, and in general they were agreed that there were no dangers attached to the taking of cannabis, and that it "Wasn't a drug of addiction". The original draft of this article was shown and discussed with them. They were surprised at the association found between cannabis taking and opiate addiction, but this in no way altered their determination to go back to taking the drug after discharge from hospital.

It seems clear that interest in cannabis is increasing among adolescents, as the recent survey among university students, carried out by Isis, has shown, and among the general population at-large, as the increase in convictions shows.

Psychiatrists have been unable to show an association between cannabis and major crime, so this may explain the confusion that exists in this country on the significance of taking cannabis. Indeed this opinion was reflected in a *Lancet* editorial in November 1963, which discussed the suggestion that marihuana be given the same legal status as alcohol, and commented that, "This suggestion is worth considering", but the general tenor of the editorial was non-committal.

## INVESTIGATION (SEE APPENDIX I.)

This investigation embodies the comments of 80 heroin and cocaine addicts on their experience of other drugs and of cannabis in particular. These addicts were seen at out-patient appointment, and some of them participated in discussions in the ward of the Addiction Unit at the hospital. Certain difficulties are met with in retrospective surveys, the more so when these matters are more a question of feeling than fact. However, there was so great a degree of uniformity that I decided to publish these results, especially as there is a widespread view that there are no dangers in the smoking of cannabis.

Nearly all addicts stopped taking cannabis when they became addicted, in the physical sense, to heroin. However, there was an interregnum, when most were taking both drugs sporadically. Those who were from the start taking heroin intravenously, very rapidly left cannabis alone, but those who were taking it intranasally or subcutaneously, were longer on both drugs. Addicts coming to a psychiatric out-patient clinic, or into hospital, remain secretive about sources of supply, and the effect of this drug. There is also a great gap between their subjective experience and that of the psychiatrist, which makes understanding difficult.

## SUBJECTIVE EFFECT OF CANNABIS

### (*a*) *Self report*

Recordings were taken of the discussions, and the remarks are taken as representative:

#### *Social implications*

"Smoking marihuana is like having a couple of pints."
"I feel crazy; would go out and have a ball."
"It has the same social implications as going for a drink, but I smoke instead."

*Effect on mood*

"It make you hypersensitive. If I feel up, I want to feel crazy."

"The lighter stuff makes you more giggly and more effective, or you think you are. It depends on the stuff. You don't worry about things, as you see them more clearly and understand them better."

*Differing drug effect*

"You can understand your immediate problems better. The darker stuff and hash makes you more introverted and sleepy. You sit in a corner and doze. You sit there giggling to yourself with a broad grin on your face."

*Jazz and art*

"You feel very lethargic. You can sit and not bother. Jazz is one of the best things that happens. You suddenly find paintings in art galleries are amusing. I like the taste and the smell."

*Dependence on preceding mood*

"Sometimes if you smoke and you're depressed it cheers you up, other times it makes you worse. It depends on the company you're with as well. If they laugh and giggle it affects you likewise, also if they are depressed."

Other more subtle effects are described: *A heightening of introspective experience.*

"You become more self-critical. Good things become more good, and bad things worse."

"I was watching an ant-heap and suddenly it became more meaningful. At other times I would have passed it by."

"It makes you relaxed, confronts you with reality."

Some *disadvantages* are noted:—

"I get depressed afterwards."

"Sometimes I get nervous after."

"Rough stuff can make your throat sore."

"It makes you lethargic if you want to do something."

"It intensified bodily feeling."

(*b*) *Report of others*

While self-report is always self-adulatory, report of others is more critical.

"I turned him on (jargon for selling or giving another a drug) and he wanted to jump out of the train. I stopped him with difficulty."

"I gave it to a woman of 36 for the first time, and she went shrieking out of the house for the police. She was a bit mad anyway."

This sort of experience seems quite frequent, and is related quite uncritically; indeed tends to cause hilarious mirth.

OBJECTIVE REPORTS

One jazz musician managed to get an illicit supply while in hospital. Apparently, while under its influence he was able to play with great success. Being no judge of his musical accomplishments, one was aware of his prolonged and frenzied playing, in a patient who had previously been inert and apathetic.

The next morning he repeated the smoke. His speech became slurred and his gait ataxic, he was repeating remarks of a boastful character, such as, "I am the greatest musician". The very ordinary remarks that he was making had to him the character of revealed truth. As an exhibition of this much-vaunted drug, the performance was most unimpressive. On the other hand, his wife who had also been indulging, was little different from normal; it was the quality of the introspective experiment that was most important to her. The husband lacked the insight into his behavior, while the wife did not.

This was a practical experiment in the taking of the drug, and demonstrates the variability of its effect from person to person, and from time to time in the same person. This has been observed repeatedly in the past and leaves open the question of tolerance to the drug. It is noteworthy that abstinence from the drug for a time seems to enhance somewhat its effect, and the initial effect of the drug is often greater than subsequently. This drug may be considered seriously intoxicating in small amounts even in habitués and seemed to leave little in the way of a hangover.

It was often possible to know that patients were taking cannabis while in hospital, because they became more lazy, they would giggle fatuously and this was not infrequently the prelude to leaving hospital altogether and relapsing to heroin again.

DIAGNOSIS

As the investigation proceeded, it became increasingly important to get objective confirmation of diagnosis. This would clearly be impossible retrospectively, but was important in the work of the Addiction Unit, in investigating abnormal behavior that might have been drug induced, or the prelude to relapse.

(*a*) *Animal Experimentation.*—(*A special animal license was obtained for this work.*)

Two rabbits were kept in the laboratory, and their urine collected for 24 hours by inserting a trap on a slope under the floor of the cages, and all urine voided was then collected in this tray. At the lower sloped end, the tray had a perforation and urine was collected into a bottle.

During a second period 20 cc of 5 per cent alcoholic extract of cannabis was added to the drinking water. Urine was collected over a further two periods of 24 hours. This latter urine was compared with the control period and with the extract of cannabis chromatographically.

The experimental design was of such a nature that it was not possible to exclude contamination of the urine by the rabbit spilling some of the drinking water into the tray. This was improbable, however, as if this had occurred the chromatogram would have resembled that of the alcoholic extract, nor did it resemble the alcoholic extract added to the urine. Hence it seems likely that the metabolized product was demonstrated in the chromatogram of rabbit urine.

(*b*) *Human volunteers*

A series of heroin addicts, who were undergoing drug withdrawal, were fed 5 per cent alcoholic extract of cannabis in doses of 15 cc and 30 cc. Urine was voided before, after, and long after the experiment. Chromatograms revealed suggestive spots. (c) The urine of patients who had recently been smoking cannabis was collected. Suggestive chromatograms are available, and this work continues.

PREVIOUS DRUG ABUSE (SEE APPENDIX II.)

This evidence must be considered unreliable. It would seem that most addicts traverse the whole field of drugs, before they finally convert to heroin. All 68 addicts born in England said they had taken cannabis, as did those from South Africa (two). Those from Canada (ten) may have started on cannabis after they came to England, and seemed more addicted to alcohol, to which they tended to relapse when they came off heroin. Amphetamines, dexamphetamines, methylamphetamines, seem to have played some part in the earliest stages of an addict's progress, as may alcohol, amphetamine-barbiturate mixtures and the barbiturates; these last are also a complication of the taking of the opiates as well as an addiction problem preceding the other addictions.

Some indication of severity may be given from preceding admissions to hospital, and there were three cases of alcoholism needing hospital admission, and two cases of amphetamine psychosis, one of phenmetrazine. The second commonest drugs were in the amphetamine-barbiturate group, although these did not lead generally to hosptial admission, and none of the cannabis takers were admitted to hospital for this drug.

ONSET OF EFFECT OF CANNABIS

Time of onset of effect seems variable; some people say they obtain a "kick" from the first smoke. Others say they had to take it for some time before they were affected; for several months before they really got a "kick". Presumably they were "social smokers" during the intervening phase.

Sooner or later there is a great effect. Most addicts describe taking about three puffs before they are affected. Others say, "My tolerance is high", and require more. The users at some stage become "stoned" or "blocked", a condition in which the person is able to participate in the conversation to some degree, but is in fact entirely self-absorbed in his own happy state. This effect of euphoria, with apparently clear consciousness (though in fact probably with some clouding), is said to be the main beneficial effect of the drug. Various

combinations of the drug with heroin are described by habitués, such as "I needed heroin to bring me down". The significance of such statements is not very clear.

MODE OF USE

The substance is bought, either as a small round lump of almost odorless, brown material, which is then gently heated and rolled into a cigarette (hashish, which is probably mainly resin), or a strawy-grass-looking material which is mixed with tobacco.

Most addicts agree that this is a social drug, and smoke it together at parties, either employing individual cigarettes or a communal cigarette. This may be passed round the gathering, being taken in turns, each person taking a puff. This method ensures the participation of those who have not previously taken the drug. The use of some hookah may be employed, and the smoke may be drawn through water, milk or even alcohol. It can be used as a snuff, and there is occasional use as a brew or tea. Many users are firmly convinced that there is some opium juice in the substance used.

Individual smoking is not uncommon, and this may have some of the characteristics of an alcoholic bout. In extreme cases, the user may smoke continually for what is described as weeks, months or even years.

The drug is bought, and therefore there exists a "pusher" or seller. He hopes, both to make money and to get his own supply free.

Finally it has use as an hypnotic. Used in bed at night before dropping off to sleep, certain of the active faction is said to be hypnotic. Burns and even fires may occur. Some addicts vigorously deny any "hangover" and others say they get a morning headache, which is relieved by aspirin.

CRIMINOGENIC EFFECT OF THE DRUG

Six out of 80 patients had convictions for "being in possession", and many more admitted to selling the drug, seeing no harm in doing this. "After all, doctor, it's not an addicting drug." The general feeling was that the situation was perhaps comparable to alcohol in the days of prohibition in the United States. That, sooner or later, opinion would change and the drug would be legalized.

From the earliest times the criminogenic effect has been described, and the word assassin was said to be derived from its earlier users. In a recent review (Andrade, 1964) (1), the conclusion was reached that "Cannabis does not have the much publicized criminogenic action", and further that, "It is necessary that cannabis cases are not handled by police measures, which do not solve, but worsen the problem".

Nevertheless, the number of police convictions in this country continues to grow. (See Table.) These measures have had the effect of making it much more difficult to obtain, and it is natural that at such times users seek substitutes, among which may be more dangerous drugs.

THE CHEMISTRY OF CANNABIS

This has been recently reviewed (Grlic, 1964) (2).

Although the substance has been used for over 2,000 years, it was only in 1942 that Woolner (3) isolated a naturally occurring tetrahydrocannabinol, which is now considered to be the major substance (THC).

About 80 derivatives of THC have been isolated by Todd and McDonald (4) in this country (1944) and all appear pharmacologically active. The maturation of the active principle is a phytochemical process and even in the same plant at one time ripening of the resin may lead to a high yield of THC and later "overripe" stage may lead to a low yield of active resins. Cannabis from tropical countries is distinguished by a high resin content and of THC: non-tropical countries give a low yield.

One of the freaks of nature has been the relatively recent discovery of the antibiotic activity of the drug (Cannabidiolic acid).

THE RELATIONSHIP BETWEEN HEROIN AND CANNABIS

It is conventional to ascribe the association of the two drugs to the mutual influence of availability in illegal society. No doubt this is one important point of contact, but there are others, which the addicts describe.

All the addicts had come through a series of preceding drug abuse, and this seemed to be more extensive the longer time one was able to yield with the patient

and gain his confidence. They were all agreed that the "best" effect was obtained from cannabis. It was for them the most enjoyable substance (until they took heroin).

The general effect of the drug resulted in more extroverted and excited behavior. Users describe it bringing them "Up to face reality". This may exacerbate the psychological and other problems that the user had to face. He may desire much more strongly to be cut off from reality, and hence seek opiates for this reason. Moreover, the effects of cannabis are not universally pleasant.

Psychotic hallucinatory episodes may occur, which are unpleasant; the feeling of being watched or being talked about; an acute anxiety or depressive episode may be precipitated; even hypomanic states, may be described as triggered off by cannabis. It would seem not to be a good protection against a depressive illness.

Six admitted to a great desire to take cannabis and to finding their avenues closed, either by the lateness of the hour or other reasons. They then describe a search for other openings. One patient alleged he tried four other places. Then, when the drug could not be obtained, he first took heroin, so did the others.

Four felt they had developed some tolerance to the effects of cannabis. They had a big habit, and after about a fortnight's continual spree they no longer got so "high". They then took heroin.

A few admitted that the effect of cannabis as an intoxicant might have "loosened some moral sense", and led to the taking of heroin. There would seem to be a group of adolescents who find that their depressive episodes are relieved by drug taking—they become essentially drug dependent.

One advanced economic motives. That in England heroin is cheaper.

These are all rationalizations after the events, but they do lead to the conclusion that there may be greater dangers in cannabis than are currently expressed, and whatever the incidence among adolescent populations they should be given a timely warning of the many dangers of drug taking in this field.

### AN ADDICTING SUBSTANCE?

This question has been often discussed. Most addicts themselves are firmly convinced that it is not addicting; some however feel that it is. Current English definitions of addiction include reference to increased tolerance and physical dependence, as manifested by a "characteristic abstinence syndrome." This has not been shown for cannabis (5). As pointed out, there are many active substances in the various samples, and it is questionable whether with our present knowledge this can be settled conclusively. The authoritative Mayoral Committee in New York (6) was certain (1944) that "marihuana was not addictive." In spite of this, many psychiatrists expressed doubt, including Kennedy and Fish (1960) (7).

Doctors need to be aware of the difficulties of fitting patients into various preconceived definitions of addiction; the most noteworthy are those of the World Health Organization in 1958 (7a) and its recent dropping of the word for drug dependence in 1964 (7b) and the earlier report of the Brain Committee in 1961 (7c). All these have emphasized the role of the drug rather than the role of the patient. There exist drugs of a very wide spectrum of addictive potential, for example, heroin. Personality factors are also important. Moreover, psychiatrists see people behaving "in an addictive way," to many unusual substances, even becoming addicted to the injections themselves (the so-called needle addiction).

To me, therefore, there are two points to tackle, that of the spectrum of the drug, its addictive potential, and the spectrum of the potential addict. There are people (described as inebriate personalities by Kolb (8)), who can become addicted to a wide variety of substances, and Partridge has described drugs as "detectors" of psychic weakness (9).

With the emphasis on physical dependence, the intoxicating effect of the substances has often been overlooked. Suppose that it be granted that there exists as yet no proven physical dependence on the drugs of the cannabis group, what if the individual becomes dependent on the euphoriant effect? Without this effect life is empty, meaningless. That everything in life is only worthwhile when seen through the "rose-tinted spectacles of this particular experience." Add to this that he or she is prepared to go to any lengths to acquire this experience. And further, that this self-indulgence is expensive, illegal and naturally makes him erratic in his work, which has little importance to him anyway. One might ask, if this person is not addicted, what is his psychiatric state?

The neuro-pharmacologist might well describe this state as one of dependence. But this is not a recognized psychiatric state. Moreover, a diabetic may well be

described as insulin-dependent or a rheumatoid as cortisone-dependent, without the psychiatric sequelae of the former condition.

In summary, therefore, addiction is a relationship between a particular person and a particular drug. Some drugs seem of high addictive potential, others low, and similarly with the persons. Quite large numbers of people seem to be able to take cannabis without showing much tolerance or physical dependence. Large numbers become dependent on the intoxicating (euphoriant) effects to such an extent that they aver they would not be willing to live without it. They would go to any lengths to get it—this in my group means that if it were not available and they were in some crisis situation they would take or resort to heroin.

Cannabis is, therefore, one of the drugs of abuse used by addicts in this country, both subsequent to other drugs of abuse such as those of the amphetamine-barbiturate mixtures, which are admittedly drugs of addiction, and also preceding the narcotic drugs, to which they predispose and which are also drugs of addiction.

Difficulties arise because most addicts aver that they are able to give up cannabis at any stage. This is also believed by most addicts about any drug (or alcoholic beverage) that they might be taking, except narcotics. Moreover, the circumstances in which the drug is taken seem of the greatest importance.

ACKNOWLEDGMENT

The animal and human experimental work briefly referred to in this article was carried out in collaboration with Dr. V. Marks, Consultant Pathologist. Area Laboratory, West Park; Dr. Fry and M. Parfitt.

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APPENDIX I

DATA CONCERNING 100 HEROIN AND COCAINE ADDICTS INCLUDING THE 80 IN THIS SERIES

| | Age— | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Under 15 | 15 to 20 | 21 to 25 | 26 to 30 | 3 to 35 | 35 to 40 | 41 to 50 | Tota |
| Males | 0 | 18 | 21 | 18 | 8 | 4 | 3 | 72 |
| Females | 0 | 6 | 10 | 7 | 5 | 0 | 0 | 28 |
| Total | 0 | 24 | 31 | 25 | 13 | 4 | 3 | 100 |

The table given in the Report to the United Nations by Her Majesty's Government, 1962, gives rather unusual age ranges. The first three rows are for total known addicts in Great Britain to narcotics. (There are no figures available for cannabis and the report since inception in 1959 has been blank for this.)

NATIONAL FIGURES

| | Age | | | | | |
|---|---|---|---|---|---|---|
| | Under 20 | 20 to 34 | 35 to 49 | 50 and over | Unknown | Total |
| Males | 3 | 89 | 64 | 96 | 10 | 262 |
| Females | 0 | 37 | 43 | 178 | 12 | 270 |
| Total | 3 | 126 | 107 | 274 | 22 | 532 |
| Addicts in this series in comparable age grouping: | | | | | | |
| Males | 10 | 55 | 6 | 1 | 0 | 72 |
| Females | 3 | 24 | 1 | 0 | 0 | 28 |
| Total | 13 | 79 | 7 | 1 | 0 | 100 |

NATIONALITY

| | British | Canadian | Jamaican | Others |
|---|---|---|---|---|
| Males | 59 | 8 | 2 | 3 |
| Females | 25 | 3 | 0 | 0 |
| Total | 84 | 11 | 2 | 3 |

APPENDIX II

PREVIOUS DRUGS TAKEN BY 80 HEROIN AND COCAINE ADDICTS

| | Cannabis | Amphetamines | Amphetamines/ Barbiturates | Barbiturates | Alcohol |
|---|---|---|---|---|---|
| Male | 51 | 6 | 23 | 5 | 18 |
| Female | 19 | 1 | 15 | 1 | 8 |
| Total | 70 | 7 | 38 | 6 | 26 |

*National table of cannabis offenses*

| Years: | *Number of offenses* |
|---|---|
| 1959 | 185 |
| 1960 | 235 |
| 1961 | 278 |
| 1962 | 588 |
| 1963 | 663 |

This Table is from that presented to the United Nations by Her Majesty's Government.

# INDEX

(NOTE.—The Senate Internal Security Subcommittee attaches no significance to the mere fact of the appearance of the name of an individual or organization in this index.)